(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2001 (10.05.2001)

PCT

(10) International Publication Number
WO 01/32604 A1

(51) International Patent Classification[7]: C07C 235/84, 235/50, 235/60, C07D 213/82, C07C 233/78, 235/82, C07D 307/68, C07C 275/36, 275/38, 275/24, A61K 31/165, 31/455, 31/34, 31/17

(21) International Application Number: PCT/GB00/04249

(22) International Filing Date:
6 November 2000 (06.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9926286.7	5 November 1999 (05.11.1999)	GB
60/201,382	2 May 2000 (02.05.2000)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

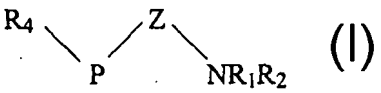
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/32604 A1

(54) Title: ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE



(I)

(57) Abstract: Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the activation of soluble guanylate cyclase, wherein: R_1 and R_2 are the same or different and each represent a C_1-C_6 alkyl group, or R_1 and R_2 together form a C_3-C_6 alkylene group; Z is a C_1-C_4 alkylene group; P is a direct bond or a moiety -X-, -Y-, -W-, -XY-, -YW- or -XYW-, wherein; W is -O-, -S-, or -NR_3, wherein R_3 is hydrogen or C_1-C_6 alkyl; Y is a moiety -U-V- wherein V is a direct bond or a C_1-C_6 alkylene group and U is -CS-, -CO-, -$S(O)_2$- or -C(=NR)- wherein R is hydrogen, hydroxy or C_1-C_6 alkyl; X is -O- or -NR_6- wherein R_6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl; and R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, a group -R-A wherein R is -(C_1-C_6 alkyl)-, -(C_2-C_6 alkenyl)- or -(C_2-C_6 alkynyl)- and A is aryl, heteroaryl, carbocyclyl or heterocyclyl, or R_4 is a group -COR", -CO_2R", -$S(O)_2$R" or -CONR'R" wherein R' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl and R" is aryl, heteroaryl, carbocyclyl or heterocyclyl.

ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE

This invention relates to activators of soluble guanylate cyclase (sGC), to their preparation and to their use.

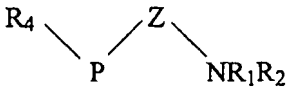
Soluble guanylate cyclase is responsible for the enzymatic conversion of guanosine-5'-triphosphate (GTP) to cyclic guanosine-3',5'-monophosphate (cGMP). The enzyme is stimulated by NO binding to the enzyme.

sGC is responsible for numerous physiological processes including vascular and non-vascular smooth muscle relaxation, peripheral and central neurotransmission, platelet reactivity and phototransduction (Hobbs A.J., TiPS, December 1997, Vol 18, p.484). Activators of sGC can therefore be expected to have valuable therapeutic properties.

As explained above, NO is known as an activator of sGC. However, this compound has a number of different physiological effects and its use in activating sGC therefore suffers from a myriad of side effects. There is therefore a need for selective activators of sGC.

3-(5'-hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1) is a known NO independent activator of sGC (Hobbs, A.J., TiPS, December 1997, Vol 18, p.484). However, the activation achieved is not high.

Accordingly, the present invention provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the activation of soluble guanylate cyclase



(I)

wherein:

- R_1 and R_2 are the same or different and each represent a C_1-C_6 alkyl group, or R_1 and R_2 together form a C_3-C_6 alkylene group;
- Z is a C_1-C_4 alkylene group;
- P is a direct bond or a moiety -X-, -Y-, -W-, -XY-, -YW- or -XYW-, wherein:
  - W is -O-, -S-, or -NR_3, wherein R_3 is hydrogen or C_1-C_6 alkyl;

- Y is a moiety -U-V- wherein V is a direct bond or a C_1-C_6 alkylene group and U is -CS-, -CO-, -$S(O)_2$- or -C(=NR)- wherein R is hydrogen, hydroxy or C_1-C_6 alkyl;
- X is -O- or -NR_6- wherein R_6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl; and
- R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, a group -R-A wherein R is -(C_1-C_6 alkyl)-, -(C_2-C_6 alkenyl)- or -(C_2-C_6 alkynyl)- and A is aryl, heteroaryl, carbocycyl or heterocyclyl, or R_4 is a group -COR″, -CO_2R″, -$S(O)_2$R″ or -CONR′R″ wherein R′ is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl and R″ is is aryl, heteroaryl, carbocyclyl or heterocyclyl.

In the moiety P, the moiety -X-, when present, is attached to R_4 and the moiety W, when present, is attached to Z. In the moiety Y, the moiety V is attached to W or, if W is not present, to Z, and the moiety U is attached to X or, if X is not present, to R_4.

As used herein, a C_1-C_6 alkyl group or moiety is a linear or branched alkyl group or moiety. Suitable alkyl groups and moieties include C_1-C_4 alkyl groups and moieties, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl. Methyl, ethyl, n-propyl and t-butyl are preferred.

A C_1-C_6 alkyl group or moiety can be substituted or unsubstituted at any position. Typically, it is unsubstituted or carries 1, 2 or 3 substituents. Suitable substituents include C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, oxo, -NR′R″ wherein R′ and R″ are the same or different and are hydrogen or C_1-C_6 alkyl, =NR, -COR, -CONR$_f$R, -CO_2R, -NR$_f$COR, -NR$_f$$CO_2$R, -NR$_f$CONR$_f$R, -$S(O)_2$R and -$S(O)_2NR_f$R wherein each R$_f$ can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and

-S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl. Further, two substituents on the same atom can, together with the atom to which they are attached, form a carbocyclyl or heterocyclyl group.

Preferred substituents include oxo, halogen, C_1-C_6 alkyl, aryl, arylthio, aryloxy, heteroaryl, heteroarylthio, heteroaryloxy and -NR'R'', =N-R, -CONHR and -$NHCO_2$R wherein R, R' and R'' are as defined above. Further, two preferred substituents on the same carbon atom may, together with the atom to which they are attached, form a carbocyclyl group, preferably a C_3-C_6 cycloalkyl group.

More preferred substituents are oxo, halogen, for example chlorine and fluorine, C_1-C_4 alkyl, for example methyl, ethyl or t-butyl, aryl, for example phenyl, -CONH-aryl, for example -CONH-phenyl, =N-aryl, for example =N-phenyl, -NH-CO_2-(C_1-C_4 alkyl), heteroarylthio, for example pyrimidinethio and -CO-aryl, for example -CO-phenyl. It is also preferred that two substituents on the same carbon atom may, together with the atom to which they are attached, form a C_3-C_6 cycloalkyl group.

As used herein, a C_2-C_6 alkenyl group or moiety is a linear or branched alkenyl group or moiety. Suitable alkenyl groups and moieties include C_2-C_4 alkenyl groups and moieties such as ethenyl, propenyl and butenyl groups and moieties. Ethenyl and propenyl are preferred. A C_2-C_6 alkenyl group or moiety may be substituted or unsubstituted at any position.

A C_2-C_6 alkenyl group is typically unsubstituted or carries 1, 2, 3 or 4 substituents. Preferably, it carries at least two substituents. Suitable substituents include oxo, C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, -NR'R'' wherein R' and R'' are the same or different and are hydrogen or C_1-C_6 alkyl, =N-R, -COR, -CONR$_f$R, -CO_2R, -NR$_f$COR, -NR$_f$$CO_2$R, -NR$_f$CONR$_f$R, -$S(O)_2$R and -$S(O)_2NR_f$R wherein each R$_f$ can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or

different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl. Further, two substituents on the same atom can, together with the atom to which they are attached, form a carbocyclyl or heterocyclyl group.

Preferred substituents include oxo, halogen, C_1-C_6 alkyl, aryl, arylthio, aryloxy, heteroaryl, heteroarylthio, heteroaryloxy and -NR'R'', =N-R, -CONHR and -$NHCO_2$R wherein R, R' and R'' are as defined above. Further, two preferred substituents on the same carbon atom may, together with the atom to which they are attached, form a carbocyclyl group, preferably a C_3-C_8 cycloalkyl group.

More preferred substituents are halogen, for example chlorine and fluorine, C_1-C_4 alkyl, for example methyl, ethyl or t-butyl, aryl, for example phenyl, heteroaryl, for example furanyl, -CONH-aryl, for example -CONH-phenyl, -NH-CO_2-(C_1-C_4 alkyl), -NH-CO-(C_1-C_4 alkyl), -NH-CO-aryl, for example -NH-CO-phenyl, heteroarylthio, for example pyrimidinethio and -CO-aryl, for example -CO-phenyl. It is also preferred that two substituents on the same carbon atom may, together with the atom to which they are attached, form a C_3-C_8 cycloalkyl group.

A C_2-C_6 alkynyl group or moiety is typically an ethynyl, propynyl or butynyl group or moiety. It may be substituted or unsubstituted at any position. Typically, it is unsubstituted or carries 1 or 2 substituents. Suitable substituents include C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, -NR'R'' wherein R' and R'' are the same or different and are hydrogen or C_1-C_6 alkyl, -COR, -CONR$_r$R, -CO_2R, -NR$_r$COR, -NR$_r$$CO_2$R, -NR$_r$CONR$_r$R, -$S(O)_2$R and -$S(O)_2NR_r$R wherein each R$_r$ can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl. Further, two substituents on the same

atom can, together with the atom to which they are attached, form a carbocyclyl or heterocyclyl group.

Preferred substituents include halogen, C_1-C_6 alkyl, aryl, arylthio, aryloxy, heteroaryl, heteroarylthio, heteroaryloxy and -CONHR and -$NHCO_2$R wherein R is as defined above. Further, two preferred substituents on the same carbon atom may, together with the atom to which they are attached, form a carbocyclyl group, preferably a C_3-C_6 cycloalkyl group.

More preferred substituents are halogen, for example chlorine and fluorine, C_1-C_4 alkyl, for example methyl, ethyl or t-butyl, aryl, for example phenyl, -CONH-aryl, for example -CONH-phenyl, -NH-CO_2-(C_1-C_4 alkyl), heteroarylthio, for example pyrimidinethio and -CO-aryl, for example -CO-phenyl. It is also preferred that two substituents on the same carbon atom may, together with the atom to which they are attached, form a C_3-C_6 cycloalkyl group.

A C_1-C_6 alkoxy group is typically a said C_1-C_6 alkyl group attached to an oxygen atom. A C_1-C_6 alkylthio group is typically a said C_1-C_6 alkyl group attached to a sulphur atom.

As used herein, a said alkylene group is a divalent alkyl moiety. It may be unsubstituted or substituted at any position. Typically, it is unsubstituted or monosubstituted. Suitable substituents include halogen, for example chlorine and flourine, hydroxy, C_1-C_4 alkyl such as methyl and ethyl, C_1-C_4 alkoxy, for example methoxy, C_1-C_4 haloalkyl, for example -CF_3 and -CCl_3 and C_1-C_4 haloalkoxy, for example -OCF_3 and -$OCCl_3$. These substituents are typically themselves unsubstituted.

A halogen is typically chlorine, fluorine, bromine or iodine. It is preferably chlorine.

A haloalkyl or haloalkoxy group is typically a said alkyl or alkoxy group substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl and haloalkoxy groups include perhaloalkyl and perhaloalkoxy groups such as -CX_3 and -OCX_3 wherein X is a said halogen atom. Particularly preferred haloalkyl groups are CF_3 and CCl_3. Particularly preferred haloalkoxy groups are -OCF_3 and -$OCCl_3$.

As used herein, an aryl group or moiety is typically a C_6-C_{20} aryl group or moiety. Suitable such aryl groups and moieties include phenyl, naphthyl and pyrenyl. Phenyl and pyrenyl are preferred.

An aryl group or moiety may be substituted or unsubstituted at any position. Typically, it is unsubstituted or carries 1, 2, 3 or 4 substituents. Suitable substituents include C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example $-CF_3$ and $-CCl_3$, C_1-C_6 haloalkoxy, for example $-OCF_3$ and $-OCCl_3$, halogen, cyano, hydroxy, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, $-NR'R''$ wherein R' and R'' are the same or different and are hydrogen or C_1-C_6 alkyl, -COR, $-CONR_/R$, $-CO_2R$, $-NR_/COR$, $-NR_/CO_2R$, $-NR_/CONR_/R$, $-S(O)_2R$ and $-S(O)_2NR_/R$ wherein each $R_/$ can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl.

Preferred substituents include C_1-C_6 alkyl, for example methyl and ethyl, C_1-C_6 alkoxy, for example methoxy, C_1-C_6 alkylthio, for example methylthio, C_1-C_6 haloalkyl, for example $-CF_3$ and $-CCl_3$, C_1-C_6 haloalkoxy, for example $-OCF_3$ and $-OCCl_3$, halogen, for example chlorine and fluorine, nitro, cyano, aryl, for example phenyl, aryloxy, for example phenyloxy, arylthio, for example phenylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, $-NR'R''$ wherein R' and R'' are the same or different and are hydrogen or C_1-C_6 alkyl, -CONH-(C_1-C_6 alkyl), -NHCONH-R wherein R is aryl, for example phenyl, or heteroaryl, $-S(O)_2NHR'$ wherein R' is aryl, for example phenyl, or heteroaryl, -S-(C_1-C_6 alkyl)-R'' wherein R'' is aryl, for example phenyl, or heteroaryl and $-COR'''$ wherein R''' is heterocycyl, heteroaryl or aryl.

Particularly preferred substituents are phenyl, in particular 4-phenyl, phenoxy, in particular 2-phenoxy, phenylthio, halogen, $-CF_3$, $-CCl_3$, nitro, cyano, $-OCF_3$, $-OCCl_3$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, -CONH-(C_1-C_4 alkyl), -CO-phenyl, $-S(O)_2NH$-phenyl, -S-(C_1-C_4 alkyl)-phenyl, -S-(C_1-C_4 alkyl)-pyrazole,

-S-(C_1-C_4 alkyl)-pyrimidine, -(C_1-C_4 alkyl)-NH-CO_2-(C_1-C_4 alkyl), thiazole, -COR wherein R is benzothiophenyl or β-carbolinyl and -NH-$(CH_2)_n$NR′R″ wherein n is from 2 to 4 and R′ and R″ are the same or different and are C_1-C_4 alkyl.

An aryl group or moiety may be fused to a further said aryl group or to a carbocyclic, heterocyclic or heteroaryl group. For example, an aryl group may be fused to a pyridine ring to form a quinoline or isoquinoline group, or to a furan ring. It may also, for example, be fused to a cyclopropyl or cyclohexyl group or to a tetrahydrofuryl group, a 1,4-dioxolane group or a pyrimidone ring, for example a 4-pyrimidone ring.

As used herein, a carbocyclic group or moiety is a non-aromatic, saturated or unsaturated carbocyclic group or moiety. Typically, it has from 3 to 10, for example from 3 to 8, carbon atoms. Preferably, it has from 3 to 8, for example 3 to 6, carbon atoms. Examples of suitable carbocyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopetadienyl, cyclohexyl, cyclohexenyl and cyclooctanyl groups. Preferred carbocyclic groups include cyclohexyl, cyclooctanyl and cyclohexenyl groups.

A carbocyclic group or moiety may be unsubstituted or substituted at any position. Typically, it carries up to 3 substituents. Suitable substituents include oxo, C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, -NR′R″ wherein R′ and R″ are the same or different and are hydrogen or C_1-C_6 alkyl, =NR, -COR, -CONR$_f$R, -CO_2R, -NR$_f$COR, -NR$_f$$CO_2$R, -NR$_f$CONR$_f$R, -$S(O)_2$R and -$S(O)_2NR_f$R wherein each R$_f$ can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R‴ and -O-(C_1-C_6 alkyl)-R‴ wherein each R‴ can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl. Further, two substituents on the same atom can, together with the atom to which they are attached, form a carbocyclyl or heterocyclyl group.

Preferred substituents include oxo, C_1-C_6 alkyl, for example methyl and ethyl, C_1-C_6 alkoxy, for example methoxy, C_1-C_6 alkylthio, for example methylthio, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, for example chlorine and fluorine, nitro, cyano, aryl, for example phenyl, aryloxy, for example phenyloxy, arylthio, for example phenythio, heteroaryl, heteroarylthio, heterocyclyl, -CONH-(C_1-C_6 alkyl), -NHCONH-R wherein R is aryl, for example phenyl, or heteroaryl, =NR′ wherein R′ is aryl, for example phenyl, or heteroaryl, -$S(O)_2NHR''$ wherein R″ is aryl, for example phenyl, or heteroaryl, -S-(C_1-C_6 alkyl)-R‴ wherein R‴ is aryl, for example phenyl, or heteroaryl, and -COR⁗ wherein R⁗ is heterocyclyl, heteroaryl or aryl.

Particularly preferred substituents are oxo, =N-aryl, for example =N-phenyl, aryl, for example phenyl, and -CO-aryl, for example -CO-phenyl.

A carbocyclic group or moiety may be fused to a further carbocyclic group or to an aryl, heteroaryl or heterocyclic group.

A heteroaryl group or moiety is typically a 5- to 10- membered aryl ring containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Preferably, the heteroaryl group or moiety is a 5- or 6- membered ring.

Suitable heteroaryl groups and moieties include pyridyl, pyranyl, furanyl, thienyl, pyrazolidinyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, furazanyl, triazolyl and thiadiazolyl groups. Pyridyl, pyrrolyl, thienyl, thiazolyl, furanyl, pyrazinyl and 1, 2, 3-thiadiazolyl groups are preferred.

A heteroaryl group or moiety may be unsubstituted or substituted at any position. Typically, it is unsubstituted or carries up to three substituents. Suitable substituents include C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, -$NR'R''$ wherein R′ and R″ are the same or different and are hydrogen or C_1-C_6 alkyl, -COR, -$CONR_fR$, -CO_2R, -NR_fCOR, -NR_fCO_2R, -NR_fCONR_fR, -$S(O)_2R$ and -$S(O)_2NR_fR$ wherein each R_f can be the same or different

and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl.

Preferred substituents include C_1-C_6 alkyl, for example methyl and ethyl, C_1-C_6 alkoxy, for example methoxy, C_1-C_6 alkylthio, for example methylthio, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, for example chlorine, cyano, nitro, aryl, for example phenyl, aryloxy, for example phenoxy, arylthio, for example phenylthio and -O-(C_1-C_6 alkyl)-R, -S-(C_1-C_6 alkyl)-R, -S-(C_1-C_6 alkyl)-CONH-R, -CO-R and -CO-NH-R, wherein R is an aryl group, for example a phenyl group.

Particularly preferred substituents include phenyl, halogen, for example chlorine, C_1-C_4 alkyl, for example methyl, -CF_3, -CCl_3, -OCF_3, -$OCCl_3$, phenylthio, phenoxy, -S-(C_1-C_4 alkyl)-CONH-phenyl, -S-(C_1-C_4 alkyl)-phenyl, -O-(C_1-C_4 alkyl)-phenyl, -CO-phenyl, cyano, C_1-C_4 alkylthio, nitro, 2,3-dihydrobenzafuranyl and -CO-NH-(1, 2, 3, 4-tetrahydranaphthalen-8-yl).

A heteroaryl group may be fused to a said aryl or carbocyclic group or to a further heteroaryl group or to a heterocyclic group. Examples of such fused heteroaryl groups include quinolyl, indolyl, isoindolyl, benzothiophenyl, imidazo[1,2-*a*]pyridyl and β-carbolinyl groups.

As used herein, a heterocyclic group or moiety is a non-aromatic, saturated or unsaturated cyclic group or moiety containing at least one, for example, one, two or three, heteroatoms selected from N, O and S. Typically, it is a 3- to 6- membered ring. Preferably, it is a 5- or 6- membered ring containing, as heteroatoms, one or two nitrogen atoms.

Suitable heterocyclic groups and moieties include pyrazolidinyl, piperidyl, piperazinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolinyl, 3,4-dihydro-2H-pyranyl, tetrahydropyrimidinyl (for example 1,2,3,4- or 1,4,5,6-tetrahydrapyrimidinyl), 2-hydropyridinyl, 2-hydrothiazolyl, tetrahydropyridinyl (for example 1,2,5,6- or 2,3,4,5-tetrahydropyridinyl) and tetrahydropyridazinyl, for example 3,4,5,6-tetrahydropyridazinyl.

A heterocyclic group or moiety may be substituted or unsubstituted at any position. Typically, it is unsubstituted or carries 1, 2, 3, 4 or 5 substituents. Suitable substituents include oxo, C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, -$NR'R''$ wherein R' and R'' are the same or different and are hydrogen or C_1-C_6 alkyl, =NR, -COR, -$CONR_rR$, -CO_2R, -NR_rCOR, -NR_rCO_2R, -NR_rCONR_rR, -$S(O)_2R$ and -$S(O)_2NR_rR$ wherein each R_r can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl. Further, two substituents on the same atom can, together with the atom to which they are attached, form a carbocyclyl or heterocyclyl group.

Preferred substituents include oxo, C_1-C_6 alkyl, for example methyl and ethyl, C_1-C_6 alkoxy, for example methoxy, C_1-C_6 alkylthio, for example methylthio, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, for example chlorine and fluorine, nitro, cyano, aryl, for example phenyl, aryloxy, for example phenyloxy, arylthio, for example phenythio, heteroaryl, heteroarylthio, heterocyclyl, -CONH-(C_1-C_6 alkyl), -NHCONH-R wherein R is aryl, for example phenyl, or heteroaryl, =NR' wherein R' is aryl, for example phenyl, or heteroaryl, -$S(O)_2NHR''$ wherein R'' is aryl, for example phenyl, or heteroaryl, -S-(C_1-C_6 alkyl)-R''' wherein R''' is aryl, for example phenyl, or heteroaryl, and -COR'''' wherein R'''' is heterocyclyl, heteroaryl or aryl.

Particularly preferred substituents are oxo, =N-aryl, for example =N-Ph, aryl, for example phenyl, halogen, C_1-C_4 alkyl, for example methyl and ethyl, C_1-C_4 alkoxy, for example methoxy and ethoxy, C_1-C_4 haloalkyl, for example -CF_3 and -CCl_3 and C_1-C_4 haloalkoxy, for example -OCF_3 and -$OCCl_3$.

Heterocyclic groups carrying one oxo substituent and up to 2, for example 0, 1 or 2, further substituents are particularly prefered.

A heterocyclic group or moiety may be fused to a further said heterocyclic group or to a said carbocyclic, aryl or heteroaryl group. Typically, it is non-fused or is fused to a benzene ring or to an iodole group. Examples of such fused heterocyclic groups include chromanyl and chromonyl groups.

An aryloxy, heteroaryloxy, heterocyclyloxy or carbocyclyloxy group is typically a said aryl, heteroaryl, heterocyclyl or carbocyclyl group attached to an oxygen atom. An arylthio, heteroarylthio, heterocyclylthio or carbocyclylthio group is typically a said aryl, heteroaryl, heterocyclyl or carbocyclyl group attached to a sulphur atom.

Typically, R_1 and R_2 are the same or different and represent methyl, ethyl, propyl, n-butyl or t-butyl. Preferably the groups represented by R_1 and R_2 are unsubstituted or carry one or two substituents. Preferred substituents for R_1 and R_2 include C_1-C_4 alkyl, for example methyl and ethyl, C_1-C_4 alkoxy, for example methoxy and ethoxy, halogen, for example chlorine, C_1-C_4 haloalkyl, for example $-CF_3$ and $-CCl_3$ and C_1-C_4 haloalkoxy, for example $-OCF_3$ and $-OCCl_3$. Typically, these substituents are themselves unsubstituted.

More preferably, R_1 and R_2 are methyl or R_1 and R_2 together form a n-butylene group.

Z is methylene, ethylene, propylene or butylene and is preferably propylene. Preferably Z is unsubstituted, monosubstituted or disubstituted. Preferred substituents for Z include C_1-C_4 alkyl, for example methyl and ethyl, C_1-C_4 alkoxy, for example methoxy and ethoxy, halogen, for example chlorine, C_1-C_4 haloalkyl, for example $-CF_3$ and $-CCl_3$ and C_1-C_4 haloalkoxy, for example $-OCF_3$ and $-OCCl_3$. Typically, these substituents are themselves unsubstituted. Particularly preferred substituents for Z are C_1-C_4 alkyl groups, in particular methyl groups. A preferred substituted alkylene group is 2,2-dimethylpropylene.

Typically, the moiety P is -Y-, -XY-, -YW- or -XYW-. Preferably, the moiety P is -XYW- or -YW-. When P is -W- or is a direct bond, R_4 is typically an aryl, heteroaryl or heterocyclyl moiety and/or is typically substituted by an aryl, heteroaryl, heterocyclyl or carbocyclyl substituent.

Typically, W is -O- or $-NR_3$. Typically, R_3 is hydrogen or is methyl, ethyl,

propyl, n-butyl or t-butyl. Preferably, R_3 is unsubstituted or carries one or two substituents. Preferred substituents for R_3 include C_1-C_4 alkyl, for example methyl and ethyl, C_1-C_4 alkoxy, for example methoxy and ethoxy, halogen, for example chlorine, C_1-C_4 haloalkyl, for example -CF_3 and -CCl_3 and C_1-C_4 haloalkoxy, for example -OCF_3 and -$OCCl_3$. Typically, these substituents are themselves unsubstituted.

More preferably, R_3 is hydrogen or methyl, most preferably hydrogen.

V is preferably a direct bond. U is preferably -CO-, -$S(O)_2$-, -C(=NH)- or -C(=NOH)-, more preferably -CO-.

X is typically -NR_6-. When X is a group -NR_6-, R_6 is typically C_1-C_4 alkyl, for example methyl, ethyl, propyl, n-butyl and t-butyl, aryl, for example phenyl, or heteroaryl, for example pyridyl. Preferably, R_6 is unsubstituted or carries 1, 2 or 3 substituents. Preferred substituents for R_6 include C_1-C_4 alkyl, for example methyl and ethyl, C_1-C_4 alkoxy such as methoxy or ethoxy, halogen, for example fluorine or chlorine, C_1-C_4 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_4 haloalkoxy, for example -OCF_3 and -$OCCl_3$, cyano, nitro and -$NR'R''$ wherein R' and R'' are the same or different and are hydrogen or C_1-C_4 alkyl. Typically, these substituents are themselves unsubstituted.

Preferably, X is -NH-.

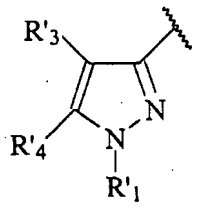
Typically, the group R_4 has up to 30 carbon atoms and up to 10 heteroatoms selected from N, O and S. Preferably, it has up to 25 carbon atoms and up to 7 heteroatoms. Typically, the group R_4 contains at least one, preferably at least two, aryl or heteroaryl rings.

Preferably, R_4 is C_1-C_6 alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, -(C_1-C_6 alkyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl or -COR'', -CO_2R'' or -$CONR'R''$ wherein R' is hydrogen or C_1-C_6 alkyl and R'' is an aryl, heteroaryl, carbocyclyl or heteroaryl group.

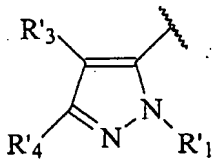
Suitable substituents for the group R_4 are oxo, C_1-C_6 alkyl, C_1-C_6 alkylthio, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, for example -CF_3 and -CCl_3, C_1-C_6 haloalkoxy, for example -OCF_3 and -$OCCl_3$, halogen, hydroxy, cyano, nitro, aryl, aryloxy, arylthio, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy,

heterocyclythio, carbocyclyl, carbocyclyloxy, carbocyclylthio, -NR'R'' wherein R' and R'' are the same or different and are hydrogen or C_1-C_6 alkyl, =NR, -COR, -CONR'R, -CO_2R, -NR'COR, -NR'CO_2R, -NR'CONR'R, -$S(O)_2$R and -$S(O)_2$NR'R wherein each R' can be the same or different and represents hydrogen or C_1-C_6 alkyl and each R can be the same or different and represents C_1-C_6 alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, and -S-(C_1-C_6 alkyl)-R''' and -O-(C_1-C_6 alkyl)-R''' wherein each R''' can be the same or different and represents aryl, heteroaryl, heterocyclyl or carbocyclyl. Further, two substituents on the same atom can, together with the atom to which they are attached, form a carbocyclyl or heterocyclyl group. Substituents on the group R_4 may be further substituted.

Typically, when P is a direct bond, -O- or -NH-, R_4 is not a moiety (A) or (B).



(A)



(B)

wherein:

R'_1 is: hydrogen, aryl, heteroaryl, 3- to 6- membered heterocyclyl, -(C_1-C_4 alkyl)-R wherein R is aryl, heteroaryl or 3- to 6- membered heterocyclyl, C_1-C_4 alkyl, -CONA'$_2$, -COA" or -SO_2A" wherein each A' is the same or different and is selected from H, C_1-C_4 alkyl and aryl and each A" is the same or different and is selected from C_1-C_4 alkyl and aryl; and

R'_3 and R'_4 are either:

(a) the same or different and selected from -CO_2A' wherein A' is as defined above, -CF_3, -CCl_3, halogen, C_1-C_4 alkoxy, -(C_1-C_4 alkyl)-aryl, -(C_1-C_4 alkyl)-heteroaryl, hydrogen, C_1-C_4 alkyl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl, -SO_2NA'$_2$ wherein A' is

as defined above, and -$CONZ_1Z_2$ wherein Z_1 and Z_2, which are the same or different, represent H, C_1-C_4 alkyl, aryl, heteroaryl, C_3-C_6 carbocyclyl, 3- to 6- membered heterocyclyl or -(C_1-C_4 alkyl)-R wherein R is aryl, heteroaryl, 3- to 6- membered heterocyclyl or C_3-C_6 carbocyclyl, or Z_1 and Z_2, together with the nitrogen atom to which they are attached, denote a 5- or 6- membered N-containing heterocyclic group; or

(b) different, one of R'_3 and R'_4 being aryl or heteroaryl and the other being as defined above

or R'_1 is as defined above and R'_3 and R'_4 together form the divalent group, -$(CH)_4$-, which group is optionally substituted.

Preferably, R_4 is not a 3- or 5- pyrazole or a 3- indazole group when P is a direct bond, -O- or -NH-. More preferably R_4 is not a pyrazole or indazole group when P is a direct bond, -O- or -NH-. More typically, R_4 is not a 3- or 5- pyrazole or a 3- indazole group or, more preferably, a pyrazole or indazole group when P does not contain the moiety U.

More preferably, when P is a direct bond, -O- or -NH- and R_4 is a heteroaryl group, R_4 is a pyridyl, pyrimidyl, thiazolyl or thienyl group. R_4 is typically also a pyridyl, pyrimidyl, thiazolyl or thienyl group when P does not contain the moiety U and R_4 is a heteroaryl group. Suitable pyridyl, pyrimidyl, thiazolyl and thienyl groups include groups fused to a said aryl or said carbocyclic group or to a said heteroaryl or said heterocyclic group. In such compounds, R_4 may be substituted by one or more of the groups mentioned above as appropriate substituents for R_4.

Preferred compounds of the invention are those in which X is -NR_6- wherein R_6 is as defined above, and R_4 is aryl or heteroaryl. In these preferred compounds, P is typically -XYW-. Y is typically -CO-. W is typically -NR_3- wherein R_3 is as defined above. X is preferably -NH- and/or R_4 is preferably phenyl, thienyl or pyrazolyl.

In the above preferred compounds, when R_4 is phenyl it is typically substituted by a phenoxy group or by a phenylthio group, in particular a 2-phenoxy or 2-phenylthio group, or by a further phenyl group, in particular a 4-phenyl group. When R_4 is thienyl or pyrazolyl, it is typically substituted by a phenyl or phenylthio group. These substituents may be unsubstituted or may be further substituted at any position. Typically, they are unsubstituted or carry one, two or three further

substituents. Preferred further substituents include halogen, for example chlorine and fluorine, C_1-C_4 alkyl, for example methyl and ethyl, C_1-C_4 alkoxy, for example methoxy and ethoxy, C_1-C_4 haloalkyl, for example -CF_3 and -CCl_3, and -$S(O)_2$NH-phenyl. These further substituents are typically themselves unsubstituted.

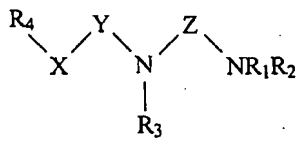
In the above preferred compounds of the invention, R_4 is preferably 2-phenoxyphenyl, 2-fluoro-diphen-4-yl, 5-(4-chlorophenylthio)-thien-3-yl, 4-(4-fluorophenyl)-thien-2-yl, 5-(4-chlorophenyl)-1-(3,4-dichlorophenyl)-pyrazol-3-yl or -(C_6H_4)-S-(C_6H_4)-$S(O)_2$-NH-(C_6H_4).

Further preferred compounds of the invention are those in which P is -YW- and R_4 is an aryl, heterocyclyl or heteroaryl group. In these further preferred compounds, Y is typically -CO-. W is typically -NR_3- wherein R_3 is as defined above. Further, R_4 is preferably an oxo-substituted heterocyclic group such as a chromonyl group or is a pyrazolyl, thienyl, phenyl or indolyl group.

In the above further preferred compounds, R_4 is typically unsubstituted or substituted by one or more, for example, one, two or three substituents selected from C_1-C_6 alkyl, for example t-butyl, phenyl, thiazolyl, phenylthio, cyano, nitro, C_1-C_6 alkylthio, for example i-propylthio, C_1-C_6 alkoxy, halogen such as chlorine and -S-(C_1-C_4 alkyl)-phenyl. These substituents may be unsubstituted or may be substituted at any position. Typically, they are unsubstituted or carry one, two or three further substituents. Preferred further substituents include halogen, for example chlorine, C_1-C_4 haloalkyl, for example -CF_3, phenyl and -$S(O)_2$-NH-phenyl. These further substituents are typically themselves unsubstituted.

Additional preferred compounds of the invention are those in which P is -W- or -YW- wherein Y is -CO- and W is -O-.

Particularly preferred compounds of the invention are compounds of formula (I′) and pharmaceutically acceptable salts thereof,

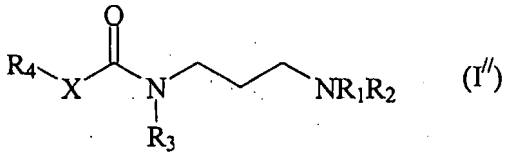


(I′)

wherein:

- R_1 and R_2 are the same or different and each represent a C_1-C_6 alkyl group, or R_1 and R_2 together form an alkylene group having from 3 to 6 carbon atoms;
- Z is an alkylene group having from 2 to 4 carbon atoms;
- R_3 is hydrogen or C_1-C_6 alkyl;
- Y is -CO- or -$S(O)_2$-;
- X is a direct bond or -NR_6- wherein R_6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl; and
- R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, a group -R-A wherein R is -(C_1-C_6 alkyl)-, -(C_2-C_6 alkenyl)- or -(C_2-C_6 alkynyl)- and A is aryl, heteroaryl, carbocycyl or heterocyclyl, or R_4 is a group -COR′ or -CO_2R′ wherein R′ is aryl, heteroaryl, carbocyclyl or heterocyclyl.

Further particularly preferred compounds of the invention are compounds of formula (I″), and pharmaceutically acceptable salts thereof



(I″)

wherein R_1 and R_2 are methyl or together form a n-butylene group, R_3 is hydrogen or methyl, R_4 is as defined in the formula (I) or in the formula (I′) and X is a direct bond or is -NR_6- wherein R_6 is as defined above. Preferably, when X in the formula (I″) is -NR_6-, R_4 is as defined as in the above preferred compounds of the invention. Preferably, when X in the formula (I″) is a direct bond, R_4 is as defined in the above further preferred compounds of the invention.

The present invention includes pharmaceutically acceptable salts of the compounds of the invention. Suitable salts include salts with pharmaceutically

acceptable acids, both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succininc, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Salts may also be formed with pharmaceutically acceptable bases such as alkali metal (eg sodium or potassium) and alkali earth metal (eg calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

Particularly preferred compounds of the invention are:

1-(3-Dimethylamino-propyl)-3-(2-phenoxy-phenyl)-urea

1-[2-(4-Chloro-phenoxy)-pyridin-3-yl]-3-(3-dimethylaminopropyl)-urea

1-(3-Dimethylamino-propyl)-3-pyren-1-ylmethyl-urea

1-(3-Dimethylamino-propyl)-3-[(1R,2R)-5-phenyl-2-(1-phenyl-methanoyl)-cyclohexyl]-urea

1-(3-Dimethylamino-propyl)-3-[2-(4-phenoxy-phenyl)-ethyl]-urea

1-(3-Dimethylamino-propyl)-3-[3-methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-urea

2'-[3-(3-Dimethylamino-propyl)-ureido]-biphenyl-2-carboxylic acid (4-fluoro-phenyl)-amide

N-(3-Chloro-4-methyl-phenyl)-4-[3-(3-dimethylamino-propyl)-ureido]-3-phenyl-butyramide

1-[4-(4-Chloro-phenylsulfanyl)-thiophen-3-yl]-3-(3-dimethylamino-propyl)-urea

1-[2-(3,4-Dimethoxy-phenyl)-6-methyl-quinolin-4-yl]-3-(4-dimethylamino-propyl)-urea

1-(6-Bromo-2-thiophen-3-yl-quinolin-4-yl)-3-(3-dimethylamino-propyl)-urea

1-[3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea

1-[6-(2,4-Dichloro-phenyl)-cyclohex-3-enyl]-3-(3-dimethylamino-propyl)-urea

1-(2-Benzylsulfanyl-phenyl)-3-(3-dimethylamino-propyl)-urea

2-{2-[3-(3-Dimethylamino-propyl)-ureido]-phenylsulfanyl}-N-phenyl-

benzenesulfonamide

1-(3-Dimethylamino-propyl)-3-(2'-fluoro-biphenyl-4-yl)-urea

N-(3,5-Dichloro-phenyl)-2-{3-[3-(3-dimethylamino-propyl)-ureido]-pyridin-2-ylsulfanyl}-acetamide

1-(3-Dimethylamino-propyl)-3-{2-[1-(1-trifluoromethyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-methanoyl]-phenyl}-urea

8-{2-[3-(3-Dimethylamino-propyl)-ureido]-phenylsulfanyl}-naphthalene-1-carboxylic acid methylamide

1-[1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridin-3-yl]-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-(3-oxo-1,2,3-triphenyl-propyl)-urea

1-[5-(4-Chloro-phenyl)-1-(3,4-dichloro-phenyl)-1*H*-pyrazol-3-yl]-3-(3-dimethylamino-propyl)-urea

1-{4-[4-(4-Chloro-phenyl)-thiazol-2-yl]-phenyl}-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-[5-(4-fluoro-phenyl)-thiophen-2-yl]-urea

1-[3-(4-*tert*-Butyl-benzyloxy)-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-[4-(4-phenyl-thiazol-2-yl)-phenyl]-urea

1-[3-(3,4-Dichloro-benzylsulfanyl)-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea

1-[2-(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-ylmethylsulfanyl)-phenyl]-3-(3-dimethylamino-propyl)-urea

1-[2-(4-Chloro-benzylsulfanyl)-3-methyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-{4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-phenyl}-urea

1-(4-Bromophenyl)-3-(3-(1-pyrrolidinyl) propyl) urea

1-(4-Bromophenyl)-3-(3-dimethylamino propyl) urea

3-(4-Bromophenyl)-1-methyl-1-(3-dimethylamino propyl) urea

1-(3-Phenyl-5-methoxy phenyl)-3-(3-dimethylamino propyl) urea

3-(4-Chlorophenyl)-1-methyl-1-(3-dimethylamino propyl) urea

1-(3-Nitrophenyl)-1-benzyl-3-(3-dimethylamino propyl) urea

1-Benzyl-1-(4-methyl-3-pyridinyl)-3-(3-dimethylamino propyl) urea

1-Methyl-1-(3,5-bistrifluoromethylphenyl)-3-(3-dimethylaminopropyl)urea

1-(2-Phenacyl-4-chorophenyl)-1-methyl-3-(3-dimethylamino propyl) urea

1-(2-Chloro-4-trifluoromethylphenyl)-3-(3-dimethylaminopropyl) urea

1-(3-Fluoro-5-trifluoromethylphenyl)-3-(3-dimethylaminopropyl) urea

1-(3-N-*tert*-butoxycarbonyl-benzylamino)-3-(3-dimethylaminopropyl) urea

N-(3-Dimethylamino-propyl)-2-[1-(4-fluorobenzoyl]-benzamide

2-[1-(4-Chlorobenzoyl]-N-(3-dimethylamino-propyl)-benzamide

5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-(2-phenylsulfamoyl-phenylsulfanyl)-benzamide

2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide

6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (3-dimethylamino -propyl)-amide

3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-nitro-benzamide

N-(3-Dimethylamino-propyl)-4-(4-phenyl-thiazol-2-yl)-benzamide

1-(3-Dimethylamino-propyl)-3-(2-phenoxyphenyl)-urea

1-[4-(4-Chloro-phenylsulfanyl)-thiophen-3-yl]-3-(3-dimethylamino-propyl) -urea

1-(3-Dimethylamino-propyl)-3-(2'-fluoro-biphenyl-4-yl)-urea

N-(3-Dimethylamino-propyl)-2-[1-(4-fluorobenzoyl]-benzamide

N-(3-Dimethylamino-propyl)-3-phenoxy-benzamide

N-(3-Dimethylamino-propyl)-2-phenoxy-benzamide

2-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-nicotinamide

4′-n-Propyl-biphenyl-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-[1-(4-Bromo-phenyl)-methanoyl]-cyclohexanecarboxylic acid (3-dimethylamino-propyl)-amide

5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid (3-dimethylamino-propyl)-amide

2-[1-(4-Chlorobenzoyl]-N-(3-dimethylamino-propyl)-benzamide

2-Phenyl-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-[1-(4-Chloro-3-nitrobenzoyl)]-N-(3-dimethylamino-propyl)-benzamide

N-(3-Dimethylamino-propyl)-2-pyren-1-yl-acetamide

N-(3-Dimethylamino-propyl)-2-[1-(3-methyl-benzo[b]thiophen-2-yl)-methanoyl]-benzamide

4-Chloro-N-(3-dimethylamino-propyl)-2-phenoxy-benzamide

N-(3-Dimethylamino-propyl)-3-(4-phenoxy-phenyl)-propionamide

N-(3-Dimethylamino-propyl)-2-[1-(1-trifluoromethyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-methanoyl]-benzamide

1-(4-Chloro-phenyl)-2,5-dimethyl-1-pyrrole-3-carboxylic acid (3-dimethylamino-propyl)-amide

2-{1-[(3-Dimethylamino-propylcarbamoyl)-methyl]-cyclopentyl}-N-(4-trifluoromethoxy-phenyl)-acetamide

8-[2-(3-Dimethylamino-propylcarbamoyl)-phenylsulfanyl]-naphthalene-1-carboxylic acid methylamide

3-Methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-1-(4-trifluoromethoxy-phenyl)-1*H*-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (3-dimethylamino-propyl)-amide

2-(Furan-2-yl)-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

Biphenyl-2,2′-dicarboxylic acid 2′-[(3-dimethylamino-propyl)-amide]-2-[(4-fluoro-phenyl)-amide]

3-Phenyl-pentanedioic acid (3-chloro-4-methyl-phenyl)-amide (3-dimethylamino-propyl)-amide

2-(3,4-Dimethoxy-phenyl)-6-methyl-quinoline-4-carboxylic acid (3-

dimethylamino-propyl)-amide

6-Bromo-(2-thiophen-3-yl)-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-nitro-benzamide

6-(2,4-Dichloro-phenyl)-cyclohex-3-ene carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-(2-phenylsulfamoyl-phenylsulfanyl)-benzamide

2'-Fluoro-[1,1'-biphenyl]-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide

Pyrazine-2,3-dicarboxylic acid 2-[(3-dimethylamino-propyl)-amide] 3-[(5,6,7,8-tetrahydro-naphthalen-1-yl)-amide]

2-[(3,5-Dichloro-phenylcarbamoyl)-methylsulfanyl]-N-(3-dimethylamino-propyl)-nicotinamide

2-(3-Trifluoromethyl-phenyl)-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(4-Chloro-phenyl)-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-1-(2,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

1-(2,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-1-(3,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

1,1-Dimethyl-indan-4-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-[1-(4-ethyl-phenyl)-methanoyl]-benzamide

N-(3-Dimethylamino-propyl)-3-(2,4,5-trimethyl-phenyl)-butyramide

2-[3-(3,4-Dichloro-phenyl)-ureido]-N-(3-dimethylamino-propyl)-benzamide

N-(3-Dimethylamino-propyl)-4-oxo-2,3,4-triphenyl-butyramide

5-(4-Chloro-phenylsulfanyl)-[1,2,3]thiadiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(3-Chloro-5-trifluoromethyl-pyridin-2-ylsulfanyl)-3-methyl-3*H*-imidazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(2-Chloro-4-trifluoromethyl-phenyl)-[1,3]-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(2,3-Dihydro-1-benzofuran-5-yl)-1,3-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(2,3-Dichloro-phenyl)-1,3-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

4-[4-(4-Chloro-phenyl)-thiazol-2-yl]-N-(3-dimethylamino-propyl)-benzamide

5-(4-Fluoro-phenyl)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-Methyl-2-(3-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (3-dimethylamino-propyl)-amide

3-(4-*tert*-Butyl-benzyloxy)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-Oxo-3-(3-trifluoromethyl-phenyl)-3,4-dihydro-phthalazine-1-carboxylic acid (3-dimethylamino-propyl)-amide

2-(4-Chloro-phenyl)-N-(3-dimethylamino-propyl)-4-oxo-4-phenyl-butyramide

5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-4-(4-phenyl-thiazol-2-yl)-benzamide

1-(2,4,5-Trichloro-phenylsulfonyl)-pyrrolidine-2-carboxylic acid (3-dimethylamino-propyl)-amide

3-(3,4-Dichloro-benzylsulfanyl)-thiophene-2-carboxylic acid (3-

dimethylamino-propyl)-amide

5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-[1-(4-fluoro-benzyl)-1*H*-indol-3-yl]-acetamide

2-Phenyl-imidazo[1,2-a]pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-(7-ethyl-1*H*-indol-3-yl)-4-oxo-4-phenyl-butyramide

Phenyl-trifluoromethyl-thieno[3,2-b]pyridine-2-carboxylic acid (3-dimethylamino-propyl)-amide

3-(4-Nitro-3-trifluoromethyl-phenoxy)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

2-(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-ylmethylsulfanyl)-N-(3-dimethylamino-propyl)-benzamide

2-(4-Chloro-benzylsulfanyl)-3-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzamide

1-(4-chlorobenzyl)-3-(2-N,N-dimethylethylamido)-6-pyridone

1-(2,6-dichlorobenzyl)-3-(3-N,N-dimethylpropylamido)-6-pyridone

1-(3-trifluoromethylbenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone

1-(2,6-dichlorobenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone

1-(3,4-dichlorobenzyl)-3-(N-[2,N,N-dimethylaminoethylamido])-2-pyridone

1-(2,6-dichlorobenzyl)-3-(N-[2-N,N-dimethylaminoethylamido])-6-pyridone

5-chloro-1-(3,4-dichlorobenzyl)-3-(2-N,N-dimethylaminoethylamido)-6-pyridone

5-chloro-3-(2-N,N-dimethylaminoethylamido)-1-(3-trifluoromethylbenzyl)-6-pyridone

5-chloro-1-(3,4-dichlorobenzyl)-3-N-(2-[N',N'-dimethylaminoethylamido])-2-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl)amido-2-pyridone

5-chloro-1-(3-trifluoromethylbenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl) amido-2-pyridone

1-benzyl-5-chloro-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido-6-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido -6-pyridone

4-(2,4-dichlorobenzoyl)pyrrole-2-N-dimethylaminopropylcarboxamide

4-[(N-[3-(N',N'-dimethylaminopropyl)]carboxamido]-2-phenylthiazole

4-(N-(3-N',N'-dimethylaminopropyl)carboxamido)-2-(4-pyridinyl)thiazole

2-[4-(N-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl-4-(3-trifluoromethylphenyl)]thiazole

4-(4-chlorophenyl)-2-(4-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl) thiazole

1-(3,5-bis(trifluoromethyl)benzyl)-3-[N-(2-dimethylaminoethyl) carboxamido]-2[1H]-pyridone

N-(3-dimethylaminopropyl)-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy) phenylsulfonamide

N1-[3-(dimethylamino)propyl]-3-[3-chloro-5-(trifluoromethyl)-2-pyridyl] propanamide

3-(N-(2-dimethylaminoethyl)carboxamido]-1-(4-trifluoromethylbenzyl))-2 [1H]-pyridone

1-ethyl-3-(3-dimethylaminopropyl)urea

1-(3-(dimethylamino)-propyl)-3-phenylurea

N1-[2-(2,4-dichlorophenoxy)phenyl]-N2-[3-(dimethylamino)propyl] ethanediamide

N4-[3-(dimethylamino)propyl]-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide

N-[[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]carbonyl]-N'-[3-(dimethylamino)propyl]urea

N-(4-chlorophenyl)-N'-[3-dimethylaminopropyl]urea

N-(3,5-Dichloro-phenyl)-3-(3-dimethylamino-propylamino)-propionamide

[3-(2-Ethyl-6-methyl-pyridin-3-yloxy)-propyl]-dimethyl-amine

8-(3-Dimethylamino-propoxy)-1,3,7-trimethyl-3,7-dihydro-purine-2,6-dione

2-(3-Dimethylamino-propylamino)-isophthalonitrile

Dimethylamino-(3-methyl-benzo[b]thiophen-2-yl)-propan-1-one (HCl)

N-Benzo[1,3]dioxol-5-ylmethyl-N,N-dimethyl-propane-1,3-diamine

N,N-Dimethyl-N-(5-nitro-quinolin-8-yl)-propane-1,3-diamine

1-(4-Chloro-phenyl)-3-(3-dimethylamino-propyl)-urea

2-Amino-N-(3-dimethylamino-propyl)-benzamide

3-Phenyl-acrylic acid 3-dimethylamino-propyl ester

3,5-Dinitro-benzoic acid 2-dimethylamino-ethyl ester

[4-(4-Bromo-phenyl)-3-(3-dimethylamino-propyl)-3H-thiazol-2-ylidene]-phenyl-amine

3-Methyl-benzofuran-2-carboxylic acid dimethylamino-dimethyl-propyl ester

N'-(2-Chloro-4-nitro-phenyl)-N,N-dimethyl-propane-1,3-diamine

[3-(3-Dimethylamino-propyl)-5-(4-nitro-phenyl)-3H-thiazol-2-ylidene]-phenyl-amine

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-dimethyl-amine

2,3-Dimethyl-1H-indole-5-carboxylic acid 2-dimethylamino-ethyl ester

N'-(3,4-Dinitro-5-pyridin-2-yl-thiophen-2-yl)-N,N-dimethyl-propane-1,3-diamine

Cyclooctyl-dithiocarbamic acid 2-dimethylamino-ethyl ester (HCl)

N-(2,6-Difluoro-phenyl)-C-dimethylamino-acetamide

2-Acetylamino-3-(4-chloro-phenyl)-N-(3-dimethylamino-propyl)-acrylamide

N-[2-[5-(4-Bromo-phenyl)-furan-2-yl]-1-(3-dimethylamino-propyl carbamoyl)-vinyl]-4-methyl-benzamide

2,6-Bis-(3-dimethylamino-propylamino)-3-nitro-benzonitrile

N-[2-(2,4-Dichloro-phenoxy)-phenyl]-N'-(3-dimethylamino-propyl)-oxalamide

3,5-Dichloro-N-(3-dimethylamino-propyl)-2,6-dimethoxy-benzamide

2-Dimethylaminomethyl-3,4-dihydro-2H-naphthalen-1-one (HCl)

2-({1-[N-(3-Dimethylamino-propyl)-3-trifluoromethyl-phenyl]-methanimidoyl}-amino)-6-fluoro-benzoic acid

2,4-Dichloro-N-(3-dimethylamino-propyl)-N'-hydroxy-benzamidine

3-(3-Methyl-ureido)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

5-Bromo-N-(3-dimethylamino-propyl)-2-hydroxy-benzamide

N-(2,4-Dichloro-phenyl)-6-(2-dimethylamino-ethylsulfanyl)-4-trifluoromethyl-nicotinamide

1-(2,6-Dichloro-benzyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide

3-Amino-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

Certain compounds of the invention are novel. Thus, the present invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, in which R_1, R_2, Z, R_3, Y, X and R_4 are as defined above except for:

2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide

N-(3-Dimethylamino-propyl)-3-phenoxy-benzamide

1-(4-chlorobenzyl)-3-(2-N,N-dimethylethylamido)-6-pyridone

1-(2,6-dichlorobenzyl)-3-(3-N,N-dimethylpropylamido)-6-pyridone

1-(3-trifluoromethylbenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone

1-(2,6-dichlorobenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone

1-(3,4-dichlorobenzyl)-3-(N-[2,N,N-dimethylaminoethylamido])-2-pyridone

1-(2,6-dichlorobenzyl)-3-(N-[2-N,N-dimethylaminoethylamido])-6-pyridone

5-chloro-1-(3,4-dichlorobenzyl)-3-(2-N,N-dimethylaminoethylamido)-6-pyridone

5-chloro-3-(2-N,N-dimethylaminoethylamido)-1-(3-trifluoromethylbenzyl)-6-pyridone

5-chloro-1-(3,4-dichlorobenzyl)-3-N-(2-[N',N'-dimethylaminoethylamido])-2-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl)amido-2-pyridone

5-chloro-1-(3-trifluoromethylbenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl) amido-2-pyridone

1-benzyl-5-chloro-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido-6-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-[N',N'-dimethylamino]ethyl) carboxamido-6-pyridone

4-(2,4-dichlorobenzoyl)pyrrole-2-N-dimethylaminopropylcarboxamide

4-[(N-[3-(N',N'-dimethylaminopropyl)]carboxamido]-2-phenylthiazole

4-(N-(3-N',N'-dimethylaminopropyl)carboxamido)-2-(4-pyridinyl)thiazole

2-[4-(N-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl-4-(3-trifluoromethylphenyl]thiazole

4-(4-chlorophenyl)-2-(4-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl) thiazole

1-(3,5-bis(trofluoromethyl)benzyl)-3-[N-(2-dimethylaminoethyl) carboxamido]-2[1H]-pyridone

N-(3-dimethylaminopropyl)-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy) phenylsulfonamide

N1-[3-(dimethylamino)propyl]-3-[3-chloro-5-(trifluoromethyl)-2-pyridyl] propanamide

3-(N-(2-dimethylaminoethyl)carboxamido]-1-(4-trifluoromethylbenzyl))-2 [1H]-pyridone

1-ethyl-3-(3-dimethylaminopropyl)urea

1-(3-(dimethylamino)-propyl)-3-phenylurea

N1-[2-(2,4-dichlorophenoxy)phenyl]-N2-[3-(dimethylamino)propyl] ethanediamide

N4-[3-(dimethylamino)propyl]-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide

N-[[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]carbonyl]-N'-[3-(dimethylamino)propyl]urea

N-(4-chlorophenyl)-N'-[3-dimethylaminopropyl]urea

N-(3,5-Dichloro-phenyl)-3-(3-dimethylamino-propylamino)-propionamide

[3-(2-Ethyl-6-methyl-pyridin-3-yloxy)-propyl]-dimethyl-amine

8-(3-Dimethylamino-propoxy)-1,3,7-trimethyl-3,7-dihydro-purine-2,6-dione

2-(3-Dimethylamino-propylamino)-isophthalonitrile

Dimethylamino-(3-methyl-benzo[b]thiophen-2-yl)-propan-1-one (HCl)

N-Benzo[1,3]dioxol-5-ylmethyl-N,N-dimethyl-propane-1,3-diamine

N,N-Dimethyl-N-(5-nitro-quinolin-8-yl)-propane-1,3-diamine

1-(4-Chloro-phenyl)-3-(3-dimethylamino-propyl)-urea

2-Amino-N-(3-dimethylamino-propyl)-benzamide

3-Phenyl-acrylic acid 3-dimethylamino-propyl ester

3,5-Dinitro-benzoic acid 2-dimethylamino-ethyl ester

[4-(4-Bromo-phenyl)-3-(3-dimethylamino-propyl)-3H-thiazol-2-ylidene]-phenyl-amine

3-Methyl-benzofuran-2-carboxylic acid dimethylamino-dimethyl-propyl ester

N'-(2-Chloro-4-nitro-phenyl)-N,N-dimethyl-propane-1,3-diamine

[3-(3-Dimethylamino-propyl)-5-(4-nitro-phenyl)-3H-thiazol-2-ylidene]-phenyl-amine

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-dimethyl-amine

2,3-Dimethyl-1H-indole-5-carboxylic acid 2-dimethylamino-ethyl ester

N'-(3,4-Dinitro-5-pyridin-2-yl-thiophen-2-yl)-N,N-dimethyl-propane-1,3-diamine

Cyclooctyl-dithiocarbamic acid 2-dimethylamino-ethyl ester (HCl)

N-(2,6-Difluoro-phenyl)-C-dimethylamino-acetamide

2-Acetylamino-3-(4-chloro-phenyl)-N-(3-dimethylamino-propyl)-acrylamide

N-[2-[5-(4-Bromo-phenyl)-furan-2-yl]-1-(3-dimethylamino-propylcarbamoyl)-vinyl]-4-methyl-benzamide

2,6-Bis-(3-dimethylamino-propylamino)-3-nitro-benzonitrile

N-[2-(2,4-Dichloro-phenoxy)-phenyl]-N'-(3-dimethylamino-propyl)-oxalamide

3,5-Dichloro-N-(3-dimethylamino-propyl)-2,6-dimethoxy-benzamide

2-Dimethylaminomethyl-3,4-dihydro-2H-naphthalen-1-one (HCl)

2-({1-[N-(3-Dimethylamino-propyl)-3-trifluoromethyl-phenyl]-methanimidoyl}-amino)-6-fluoro-benzoic acid

2,4-Dichloro-N-(3-dimethylamino-propyl)-N'-hydroxy-benzamidine

3-(3-Methyl-ureido)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

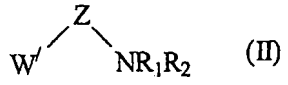
5-Bromo-N-(3-dimethylamino-propyl)-2-hydroxy-benzamide

N-(2,4-Dichloro-phenyl)-6-(2-dimethylamino-ethylsulfanyl)-4-trifluoromethyl-nicotinamide

1-(2,6-Dichloro-benzyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide

3-Amino-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

Compounds of the invention in which P is -U-W- may be prepared by reacting a compound of formula (II)



(II)

wherein Z, R_1 and R_2 are as defined above and W′ is a group WH wherein W is as defined above, with a compound of formula (III)

$$R_4—U' \qquad \text{(III)}$$

wherein R_4 is as defined above and U′ is a group -UL wherein U is as defined above and L is a hydroxy group or a leaving group such as a halogen atom.

Compounds of formulae (II) and (III) are known compounds, or may be prepared by analogy with known methods.

Typically, the reaction takes place in the presence of a base such as diisopropylethylamine or the equivalent polymer bound resin *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), and a coupling agent such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU). The reaction typically takes place in a solvent such as acetonitrile at a temperature of from 0 to 100 °C, preferably from 20 to 80 °C. The work-up typically involves the use of a sequestration enabling reagent such as tetrafluorophthalic anhydride and polymer bound scavenger resins to remove unwanted starting materials. Such techniques are described in Parlow *et al* Tetrahedron Lett., 1997, **38**, 7959.

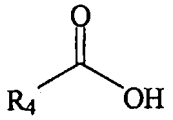
Compounds of the invention wherein P is -NH-CO-W- can be prepared by reacting a compound of formula (II) above with a compound of formula (IV)

$$R_4 — N=C=O \qquad (IV)$$

wherein R_4 is as defined above.

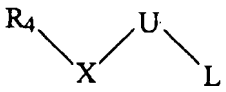
Typically, the reaction takes place in a hydrocarbon solvent such as toluene at a temperature of from 0 to 100 °C. The work-up typically involves the use of a sequestration enabling reagent such as tetrafluorophthalic anhydride and polymer bound scavenger resins to remove unwanted starting materials. The amides thereby prepared may be converted to the corresponding amidines by standard methods.

The compounds of formula (IV) may be prepared by techniques known in the art. For example, they may be prepared by reacting a compound of formula (V)


(V)

wherein R_4 is as defined above, with diphenylphosphoryl azide (DPPA), in the presence of a base such as triethylamine. Typically, the reaction takes place under reflux, in a solvent such as toluene. Compounds of formula (V) are known compounds or may be prepared by analogy with known methods.

Compounds of the invention wherein P is -X-U-W- wherein X, U and W are as defined above can be prepared by reacting a compound of formula (II) above with a compound of formula (VI)


(VI)

wherein R_4, X and U are as defined above and L is a hydroxy group or leaving group such as a 4-nitro-phenoxy group. Typically, the reaction takes place in a hydrocarbon solvent such as tetrahydrofuran at a temperature of from 60 to 70 °C. The work-up typically involves the use of a sequestration enabling reagent such as tetrafluorophthalic anhydride and polymer bound scavenger resins to remove unwanted starting material.

The compounds of formula (VI) are known compounds or may be prepared by analogy with known methods. For example, compounds of formula (VI) in which U is -CO- can be prepared by reacting a compound of formula (VII)

R_4XH (VII)

wherein R_4 and X are as defined above, with a chloroformate, for example an aromatic chloroformate such as 4-nitrophenyl chloroformate. Typically, the reaction takes place under reflux, in a solvent such as anhydrous THF. Further, compounds of formula (VI) in which U is -C-(=NH)- can, for example, be prepared from the corresponding nitrile of formula R_4-X-C≡N, for example by reaction with hydrochloric acid.

Compounds of the invention in which P is -X-Y- or -X-Y-W- and R_4 is other than -COR″, -CO_2R″, -$S(O)_2$R″ and -CONR′R″ can be made by standard techniques, for example by reacting a compound of formula (VIII)

$$R_4\text{-X-H} \qquad \text{(VIII)}$$

wherein R_4 is other than -COR″, -CO_2R″, $S(O)_2$R″ and -CONR′R″ and X is as defined above, with a compound of formula (IX)

$$\text{L-Y-ZNR}_1\text{R}_2 \qquad \text{(IX)}$$

wherein Y, Z, R_1 and R_2 are as defined above and L represents a hydroxy group or a leaving group such as a halogen. The reaction is typically conducted in the presence of a base at from -78°C to the reflux temperature of the solvent.

The compounds of formulae (VIII) and (IX) are known compounds or may be prepared by analogy with known methods.

Compounds of the invention in which P is -X-U-W- and R_4 is -COR″, -CO_2R″, -$S(O)_2$R″ or -CONR′R″ can be made in an analogous fashion by reacting a compound of formula (X)

$$R_4\text{X-U-L} \qquad \text{(X)}$$

wherein R_4, X and U are as defined above and L represents a hydroxy group or a leaving group such as a halogen, with a compound of formula (XI)

$HWZNR_1R_2$ (XI)

wherein W, Z, R_1 and R_2 are as defined above.

The compounds of formula (X) and (XI) are known compounds or may be prepared by analogy with known methods.

Compounds in which P is X or W and R_4 is other than -COR″, $-CO_2R''$, $-S(O)_2R''$ and -CONR′R″ can be prepared, for example, by reacting a compound of formula (XII)

R_4-AH (XII)

wherein A is -X- or -W-, wherein X and W are as defined above and R_4 is other than -COR″, $-CO_2R''$, $-S(O)_2R''$ and -CONR′R″, with a compound of formula (XIII)

$L\text{-}Z\text{-}NR_1R_2$ (XIII)

wherein Z, R_1 and R_2 are as defined above and L is a leaving group such as a triflate group or a halogen atom. The reaction can be conducted under standard conditions. Typically, it takes place in the presence of a base in a solvent such as DMF.

The compounds of formula (XII) are known compounds or may be prepared by analogy with known methods. The compounds of formula (XIII) are also known compounds or may be prepared by analogy with known methods. For example, they can be prepared from a corresponding compound of formula $HO\text{-}Z\text{-}NR_1R_2$ by reaction with triflic anhydride or with PCl_5.

Compounds of the invention in which P is X or W and R_4 is -COR″, $-CO_2R''$, $-S(O)_2R''$ or CONR′R″ can be prepared by reacting a compound of formula (IXV)

$HA\text{-}Z\text{-}NR_1R_2$ (IXV)

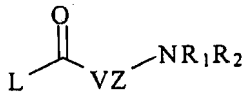
wherein A, Z, R_1 and R_2 are as defined above, with R_4-L, wherein R_4 is as defined above and L is a hydroxy group or a leaving group, for example a halogen. The reaction can be conducted under standard conditions, such as those given above for the reaction of compounds of formulae (VIII) and (IX).

Compounds of formula (IXV) and compounds of formula R_4-L are known compounds or may be prepared by analogy with known methods.

Compounds of the invention in which P is Y, Y is -CO- and R_4 is aryl or heteroaryl may be prepared, for example, by a Friedel-Crafts reaction between a compound of formula (XV)

$$R_4\text{-}H \qquad (XV)$$

wherein R_4 is aryl or heteroaryl, and a compound of formula (XVI)

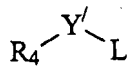


(XVI)

wherein L is a hydroxy group, a group OR wherein R is alkyl, or a halogen, for example chlorine, and Z, V, R_1 and R_2 are as defined above. The reaction can be performed under conventional conditions, in the presence of a catalyst such as $AlCl_3$. Examples of such reactions are described in section 1-15 of "Advanced Organic Chemistry", 3rd Edition, by Jerry March.

The compounds of formulae (XV) and (XVI) are known compounds or may be prepared by analogy with known methods.

Compounds in which P is -Y- or -XY- and in which X, Y and R_4 are as defined above may be prepared, for example, by reacting a compound of formula (XVII)



(XVII)

wherein R_4 is as defined above, Y' is -U- or -X-U-, and L is a hydroxy group or a leaving group, for example a halogen atom, with an organometallic compound of formula (XVIII)

$$M\text{-}B\text{-}NR_1R_2 \quad \text{(XVIII)}$$

wherein B is -V-Z- wherein V and Z are as defined above, R_1 and R_2 are as defined above and M is a metal-containing moiety such as Li or -MgX wherein X is a halogen atom such as bromine.

The reaction can be carried out under conventional conditions. Preferably, M in the formula (XVIII) is Li. When M in the formula (XVIII) is -MgX, it may be necessary to conduct the reaction at around -78 °C and to use a large excess of the compound of formula (XVII).

The compounds of formula (XVII) are known compounds or may be prepared by analogy with known methods. The compounds of formula (XVIII) are also known compounds or may be prepared by analogy with known methods. For example, compounds of formula (XVIII) in which M is Li can be prepared by reacting a corresponding compound of formula $Br\text{-}B\text{-}NR_1R_2$ with lithium or with magnesium.

In some cases, it may be necessary to protect the $-NR_1R_2$ group during the synthesis of the compounds of formula (XVIII) or during the reaction between the compounds of formulae (XVIII) and (XVII). This can be done by standard techniques.

Compounds of the invention in which P is -Y-W- or -XYW-, wherein Y is -UV- and -V- is -(C_1-C_6 alkyl)-, can be made, for example, by reacting a compound of formula (IXX)

$$R_4\text{-}P\text{-}L \quad \text{(IXX)}$$

wherein R_4 and P are as defined above and L is a leaving group such as a halogen atom or a triflate group, with a compound of formula (XX)

$$HW\text{-}ZNR_1R_2 \qquad (XX)$$

wherein W, Z, R_1 and R_2 are as defined above. The reaction can be conducted under conventional conditions. Typically, it is conducted in the presence of a base. If necessary, the NR_1R_2 group can be protected during the reaction by conventional means.

The compounds of formulae (IXX) and (XX) are knowN compounds, or may be prepared by analogy with known methods. For example, the compounds of formula (IXX) can be prepared by reacting a corresponding compound of formula R_4-P-OH with triflic anhydride or PCl_5.

Compounds in which P is a direct bond can be prepared by conventional synthetic techniques.

A compound of the invention can, of course, be converted to a different compound of the invention by standard functional group interconversions known to those of skill in the art. For example, a compound of the invention in which U is -CO- can be converted to a compound of the invention in which U is -C(=NR)- by reaction with a compound of formula RNH_2. Suitable such reactions are described in section 6-14 of "Advanced Organic Chemistry" 3rd Edition, by Jerry March.

Pharmaceutically acceptable salts of the compounds of formula (I) may be prepared by salifying a compound of formula (I) with an appropriate acid or base.

The compounds of the invention are activators of sGC. They can be used as selective sGC activators. A compound of the invention can therefore be used as a vasodilator or to inhibit platelet aggregation. It can be used for the treatment or prevention of peripheral vascular diseases such as hypertension, angina pectoris, arteriosclerosis, or for the treatment or prevention of glaucoma, preeclampsia, Raynaud's Syndrome, stroke or erectile dysfunction. Further, the compounds of the invention are effective in improving ocular blood flow. They can therefore be used

in the treatment and prevention of age-related macular degeneration (AMD). For example, they can be used in the treatment and prevention of non-exudative or exudative AMD. They can also be used in the treatment and prevention of neovascular or non-neovascular AMD.

Conditions attributable to down regulation of sGC can thus be alleviated.

Accordingly, the present invention also provides a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body, wherein R_1, R_2, Z, R_3, Y, X and R_4 are as defined above.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, either subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

A compound of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural

gum, agar, sodium alginte, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for intravenous or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical daily dose is from about 0.1 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated , the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

The Examples which follow illustrate the invention.

EXAMPLES

The synthesis of some of the compounds of the invention is detailed below.

Examples 1 to 69

The aryl acid (different for each reaction) (0.1 mmol), 3-(dimethylamino)-propylamine (10 mg, 0.1 mmol), *N*, *N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (86.0 mg, 0.3 mmol, loading 3.5 mmol/g) and *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N*, *N*-tetramethyluronium hexafluorophosphate (HATU) (38 mg, 0.1 mmol) were shaken under nitrogen in anhydrous acetonitrile (4 mL) and heated to 50 °C for 5 hours. After this time the reaction mixture was cooled to room temperature.

Tetrafluorophthalic anhydride (65 mg, 0.3 mmol) was then added and the reaction mixture was shaken under nitrogen for 18 hours. Macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate), (610 mg, 1.96 mmol, loading 3.18 mmol/g) was then added and the reaction mixture was shaken under nitrogen for a further 48 hours. The reactions were then filtered through filter syringes into vials and washed with methanol. The solvent was removed on a vacuum concentrator and each product was weighed and analysed by LC-MS.

This method was used to synthesise the following compounds. The molecular weight, purity and yield of the compounds synthesised is shown in Table 1.

Example No.	Compound
1	N-(3-Dimethylamino-propyl)-2-[1-(4-fluorobenzoyl]-benzamide (CFM2262)
2	N-(3-Dimethylamino-propyl)-3-phenoxy-benzamide (CFM2263)
3	N-(3-Dimethylamino-propyl)-2-phenoxy-benzamide (CFM2264)
4	2-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-nicotinamide (CFM2265)
5	4′-n-Propyl-biphenyl-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2266)

6	2-[1-(4-Bromo-phenyl)-methanoyl]-cyclohexanecarboxylic acid (3-dimethylamino-propyl)-amide(CFM2267)
7	5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2268)
8	2-[1-(4-Chlorobenzoyl]-N-(3-dimethylamino-propyl)-benzamide (CFM2269)
9	2-Phenyl-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2331)
10	2-[1-(4-Chloro-3-nitrobenzoyl)]-N-(3-dimethylamino-propyl)-benzamide (CFM2332)
11	N-(3-Dimethylamino-propyl)-2-pyren-1-yl-acetamide (CFM2333)
12	N-(3-Dimethylamino-propyl)-2-[1-(3-methyl-benzo[b]thiophen-2-yl)-methanoyl]-benzamide (CFM2320)
13	4-Chloro-N-(3-dimethylamino-propyl)-2-phenoxy-benzamide (CFM2321)
14	N-(3-Dimethylamino-propyl)-3-(4-phenoxy-phenyl)-propionamide (CFM2322)
15	N-(3-Dimethylamino-propyl)-2-[1-(1-trifluoromethyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-methanoyl]-benzamide (CFM2334)
16	1-(4-Chloro-phenyl)-2,5-dimethyl-1-pyrrole-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2335)
17	2-{1-[(3-Dimethylamino-propylcarbamoyl)-methyl]-cyclopentyl}-N-(4-trifluoromethoxy-phenyl)-acetamide (CFM2336)
18	8-[2-(3-Dimethylamino-propylcarbamoyl)-phenylsulfanyl]-naphthalene-1-carboxylic acid methylamide (CFM2337)
19	3-Methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-1-(4-trifluoromethoxy-phenyl)-1*H*-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2338)

20	6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2339)
21	2-(Furan-2-yl)-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2340)
22	Biphenyl-2,2′-dicarboxylic acid 2′-[(3-dimethylamino-propyl)-amide]-2-[(4-fluoro-phenyl)-amide] (CFM2342)
23	3-Phenyl-pentanedioic acid (3-chloro-4-methyl-phenyl)-amide (3-dimethylamino-propyl)-amide (CFM2343)
24	2-(3,4-Dimethoxy-phenyl)-6-methyl-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2344)
25	6-Bromo-(2-thiophen-3-yl)-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2345)
26	3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2346)
27	4-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-nitro-benzamide (CFM2347)
28	6-(2,4-Dichloro-phenyl)-cyclohex-3-ene carboxylic acid (3-dimethylamino-propyl)-amide (CFM2348)
29	N-(3-Dimethylamino-propyl)-2-(2-phenylsulfamoyl-phenylsulfanyl)-benzamide(CFM2349)
30	2'-Fluoro-[1,1'-biphenyl]-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2350)
31	2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide (CFM2351)
32	Pyrazine-2,3-dicarboxylic acid 2-[(3-dimethylamino-propyl)-amide] 3-[(5,6,7,8-tetrahydro-naphthalen-1-yl)-amide] (CFM2352)
33	2-[(3,5-Dichloro-phenylcarbamoyl)-methylsulfanyl]-N-(3-dimethylamino-propyl)-nicotinamide (CFM2432)

34	2-(3-Trifluoromethyl-phenyl)-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2368)
35	2-(4-Chloro-phenyl)-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2369)
36	5-Chloro-1-(2,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2370)
37	1-(2,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2371)
38	5-Chloro-1-(3,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2372)
39	1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2373)
40	5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2388)
41	1,1-Dimethyl-indan-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2389)
42	N-(3-Dimethylamino-propyl)-2-[1-(4-ethyl-phenyl)-methanoyl]-benzamide (CFM2390)
43	N-(3-Dimethylamino-propyl)-3-(2,4,5-trimethyl-phenyl)-butyramide (CFM2391)
44	2-[3-(3,4-Dichloro-phenyl)-ureido]-N-(3-dimethylamino-propyl)-benzamide (CFM2392)
45	N-(3-Dimethylamino-propyl)-4-oxo-2,3,4-triphenyl-butyramide (CFM2393)
46	5-(4-Chloro-phenylsulfanyl)-[1,2,3]thiadiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2394)
47	2-(3-Chloro-5-trifluoromethyl-pyridin-2-ylsulfanyl)-3-methyl-3*H*-imidazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2395)

48	2-(2-Chloro-4-trifluoromethyl-phenyl)-[1,3]-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2396)
49	2-(2,3-Dihydro-1-benzofuran-5-yl)-1,3-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2397)
50	2-(2,3-Dichloro-phenyl)-1,3-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2398)
51	4-[4-(4-Chloro-phenyl)-thiazol-2-yl]-N-(3-dimethylamino-propyl)-benzamide (CFM1899)
52	5-(4-Fluoro-phenyl)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2399)
53	4-Methyl-2-(3-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2400)
54	3-(4-*tert*-Butyl-benzyloxy)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2401)
55	4-Oxo-3-(3-trifluoromethyl-phenyl)-3,4-dihydro-phthalazine-1-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2402)
56	2-(4-Chloro-phenyl)-N-(3-dimethylamino-propyl)-4-oxo-4-phenyl-butyramide (CFM2403)
57	5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2404)
58	N-(3-Dimethylamino-propyl)-4-(4-phenyl-thiazol-2-yl)-benzamide (CFM2405)
59	1-(2,4,5-Trichloro-phenylsulfonyl)-pyrrolidine-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2406)
60	3-(3,4-Dichloro-benzylsulfanyl)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2407)
61	5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2408)

62	N-(3-Dimethylamino-propyl)-2-[1-(4-fluoro-benzyl)-1*H*-indol-3-yl]-acetamide (CFM2409)
63	2-Phenyl-imidazo[1,2-a]pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2410)
64	N-(3-Dimethylamino-propyl)-2-(7-ethyl-1*H*-indol-3-yl)-4-oxo-4-phenyl-butyramide (CFM2411)
65	Phenyl-trifluoromethyl-thieno[3,2-b]pyridine-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2412)
66	3-(4-Nitro-3-trifluoromethyl-phenoxy)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2428)
67	2-(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-ylmethylsulfanyl)-N-(3-dimethylamino-propyl)-benzamide (CFM2429)
68	2-(4-Chloro-benzylsulfanyl)-3-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2430)
69	N-(3-Dimethylamino-propyl)-4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzamide (CFM2431)

Table 1

Example	Molecular Weight	LC-MS Results % Purity	Yield (mg)	% Yield
1	328.22	62.1	25.5	40
2	298.22	86.6	23.7	41
3	298.22	86.1	32.1	55
4	333.64	96.6	33	51
5	324.3	100	35.1	55
6	395.17	60.1	33.5	43
7	340.18	95.7	14.2	21
8	344.68	58.5	25.2	37
12	380.35	90.5	32.2	43
13	332.67	73.8	24.5	38
14	326.28	96.1	21.2	33
9	333.27	94.0	22.6	35
10	389.68	94.4	43.8	57
11	344.3	44.0	46.1	68
15	472.35	96.2	50.9	>100
16	333.7	87.0	24.3	74
17	429.35	71.6	30.1	71
18	421.4	52.4	28.7	69
19	468.34	72.4	28.1	61
20	386.37	68.0	10.8	28
21	323.23	92.9	12.8	40
22	350.1	90.8	22.5	65
23	415.8	52.0	17	41
24	407.35	90.5	15.5	38
25	418.19	69.5	13.1	32
26	435.88	95.9	21.3	43
27	377.67	83.6	12.8	33
28	355.15	59.0	16.8	48
29	469.46	72.9	21.9	74
30	300.24	93.1	11.5	35
31	328.31	63.4	16	34
32	381.32	57.0	17.1	45
34	357.24	97.3	14.1	40
35	323.68	96.9	17.7	55
36	416.57	94.1	10.1	25
37	382.13	86.0	14	37

38	416.57	88.9	12.8	31
39	382.13	64.5	10.3	27
40	416.57	100	22.6	55
41	274.24	97.4	12.3	45
42	338.28	89.0	16.7	50
43	290.28	81.6	15.7	55
44	409.15	91.9	12.1	30
45	414.38	41.0	18.8	47
46	356.73	86.6	20.3	58
47	421.71	79.9	14.3	34
48	391.68	90.9	25	72
49	331.27	91.2	24.5	20
50	358.13	34.2	16.3	75
52	306.24	96.4	18.3	44
53	371.26	97.4	27.6	60
54	374.38	94.8		75
55	418.26	96.7	26.2	71
56	372.73	34.4	21	51
57	382.73	100	19.9	54
58	365.34	100	26.3	69
59	442.63	96.6	16.2	45
60	403.23	100	27.8	63
61	355.71	100	19.9	50
62	367.71	100	8.9	25
63	322.25	54.6	26.2	66
64	405.38	97.8	21.2	53
65	407.3	100	11.5	50
66	417.24	79.5	19.7	48
67	442.85	59.7	5.1	12
68	444.82	32.7	18.9	43
69	436.41	86.3	23.6	55
33	441.22	40.3	18.2	42

Examples 70 to 99

The aryl acid (different for each reaction) (0.1 mmol) was stirred under nitrogen in anhydrous toluene (2 mL) and heated to 50 °C. Triethylamine (10 mg, 0.1 mmol) dissolved in 1 mL of anhydrous toluene was then added. The temperature was raised to 80 °C and diphenylphosphorylazide (DPPA), (27.0 mg, 0.1 mmol) was added.

The reaction was kept at this temperature for 1 hour then cooled to room temperature while still stirring under nitrogen.

3-(Dimethylamino)-propylamine (10 mg, 0.1 mmol) was added and the whole mixture was stirred at room temperature overnight. Tetrafluorophthalic anhydride (64.7 mg, 0.3 mmol) was added and the reaction stirred for a further 18 hours. Following this 20 equivalents of macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate), (610 mg, 1.96 mmol) was added and the reactions were stirred for another 24 hours. Each reaction was then filtered through filter syringes into vials and washed with methanol. The solvent was removed using a vacuum concentrator and each product was weighed and analysed by LC-MS.

This method was used to synthesise the following compounds. The molecular weight, purity and yield of the compounds synthesised is shown in Table 2.

Examples No.	Compounds
70	1-(3-Dimethylamino-propyl)-3-(2-phenoxy-phenyl)-urea (CFM2260)
71	1-[2-(4-Chloro-phenoxy)-pyridin-3-yl]-3-(3-dimethylaminopropyl)-urea (CFM2261)
72	1-(3-Dimethylamino-propyl)-3-pyren-1-ylmethyl-urea (CFM2317)
73	1-(3-Dimethylamino-propyl)-3-[(1R,2R)-5-phenyl-2-(1-phenyl-methanoyl)-cyclohexyl]-urea (CFM2318)
74	1-(3-Dimethylamino-propyl)-3-[2-(4-phenoxy-phenyl)-ethyl]-urea (CFM2319)
75	1-(3-Dimethylamino-propyl)-3-[3-methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-urea (CFM2353)
76	2'-[3-(3-Dimethylamino-propyl)-ureido]-biphenyl-2-carboxylic acid (4-fluoro-phenyl)-amide (CFM2354)
77	N-(3-Chloro-4-methyl-phenyl)-4-[3-(3-dimethylamino-propyl)-ureido]-3-phenyl-butyramide (CFM2355)

78	1-[4-(4-Chloro-phenylsulfanyl)-thiophen-3-yl]-3-(3-dimethylamino-propyl)-urea (CFM2356)
79	1-[2-(3,4-Dimethoxy-phenyl)-6-methyl-quinolin-4-yl]-3-(4-dimethylamino-propyl)-urea (CFM2357)
80	1-(6-Bromo-2-thiophen-3-yl-quinolin-4-yl)-3-(3-dimethylamino-propyl)-urea (CFM2358)
81	1-[3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea (CFM2359)
82	1-[6-(2,4-Dichloro-phenyl)-cyclohex-3-enyl]-3-(3-dimethylamino-propyl)-urea (CFM2360)
83	1-(2-Benzylsulfanyl-phenyl)-3-(3-dimethylamino-propyl)-urea (CFM2361)
84	2-{2-[3-(3-Dimethylamino-propyl)-ureido]-phenylsulfanyl}-N-phenyl-benzenesulfonamide (CFM2362)
85	1-(3-Dimethylamino-propyl)-3-(2'-fluoro-biphenyl-4-yl)-urea (CFM2363)
86	N-(3,5-Dichloro-phenyl)-2-{3-[3-(3-dimethylamino-propyl)-ureido]-pyridin-2-ylsulfanyl}-acetamide (CFM2364)
87	1-(3-Dimethylamino-propyl)-3-{2-[1-(1-trifluoromethyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-methanoyl]-phenyl}-urea (CFM2366)
88	8-{2-[3-(3-Dimethylamino-propyl)-ureido]-phenylsulfanyl}-naphthalene-1-carboxylic acid methylamide (CFM2367)
89	1-[1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridin-3-yl]-3-(3-dimethylamino-propyl)-urea (CFM2413)
90	1-(3-Dimethylamino-propyl)-3-(3-oxo-1,2,3-triphenyl-propyl)-urea (CFM2414)
91	1-[5-(4-Chloro-phenyl)-1-(3,4-dichloro-phenyl)-1*H*-pyrazol-3-yl]-3-(3-dimethylamino-propyl)-urea (CFM2415)
92	1-{4-[4-(4-Chloro-phenyl)-thiazol-2-yl]-phenyl}-3-(3-dimethylamino-propyl)-urea (CFM2416)
93	1-(3-Dimethylamino-propyl)-3-[5-(4-fluoro-phenyl)-thiophen-2-yl]-urea (CFM2417)
94	1-[3-(4-*tert*-Butyl-benzyloxy)-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea (CFM2418)

95	1-(3-Dimethylamino-propyl)-3-[4-(4-phenyl-thiazol-2-yl)-phenyl]-urea (CFM2419)
96	1-[3-(3,4-Dichloro-benzylsulfanyl)-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea (CFM2420)
97	1-[2-(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-ylmethylsulfanyl)-phenyl]-3-(3-dimethylamino-propyl)-urea (CFM2433)
98	1-[2-(4-Chloro-benzylsulfanyl)-3-methyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-3-(3-dimethylamino-propyl)-urea (CFM2434)
99	1-(3-Dimethylamino-propyl)-3-{4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-phenyl}-urea (CFM2435)

Table 2

Example	Molecular Weight of Product	LC-MS Results % Product	Yield (mg)	% Yield
70	313.22	57.53	51	83.06
71	348.64	56.3	41.4	60.6
72	359.3	58.85	108.7	>100
73	407.38	42.59	75.1	94.1
74	341.28	54.28	52.1	77.9
87	487.35	53.05	29.4	61.44
88	436.4	53.98	63.6	>100
75	483.34	42	41.8	87.45
76	434.34	76.93	26	60.48
77	430.8	31.66	34.5	80.98
78	369.76	74.31	36.3	99.18
79	422.35	26.75	36.7	87.79
80	433.19	69.82	32.4	75.55
81	450.88	32	27.3	61.31
82	370.15	38.84	29.1	79.42
83	343.31	100	32.2	94.46
84	484.46	36.4	15.8	32.94
85	315.21	56.84	23.3	74.68
86	456.22	38.85	58.6	>100
89	397.13	32.11	46.1	>100
90	429.38	35.0	51.0	>100
91	466.62	51.18	45.7	98.6
92	414.78	70.68	65.8	>100
93	321.24	48.83	20.5	65.12
94	389.38	44.0	41.8	>100
95	380.34	49.46	33.5	89.88
96	418.23	27.0	32.8	80
97	457.85	52.98	47.1	>100
98	459.82	60.47	65.9	>100
99	451.41	55.72	19.9	44.53

Example 100

1-(4-Bromophenyl)-3-(3-(1-pyrrolidinyl) propyl) urea (CFM2138)

4-Nitrophenyl chloroformate (87.0 mg, 0.436 mmol), 4-bromoaniline (50.0 mg, 0.29 mmol) and triethylamine (44.0 mg, 0.436 mmol) were refluxed under nitrogen in

anhydrous THF (20 mL) for 18 hours. After this time 1-(3-aminopropyl) pyrrolidine (55.0 mg, 0.436 mmol) was added and the whole reaction mixture was refluxed for a further 2 hours.

The reaction mixture was cooled to room temperature and tetrafluorophthalic anhydride (191.0 mg, 0.87 mmol) was added. The reaction was stirred at room temperature under nitrogen for 1 hour, then 6 equivalents of tris-(2-aminoethyl)amine polystyrene resin (PS-trisamine), (500 mg, 1.74 mmol, loading 3.5 mmol/g) was added and the reaction stirred for 2 hours. Following this 20 equivalents of Dowex AG1 resin (OH^- form) (1.68 g, 5.8 mmol, loading 3.45 mmol/g) was added and the mixture was stirred for 18 hours at room temperature.

It should be noted that the Cl^- form of the resin was converted to the OH^- form by washing with 20 volumes of 1M NaOH solution, followed by distilled water until the washings are neutral. Another 20 equivalents of the resin was added after this time and the reaction was stirred for a further 2 hours. The reaction mixture was then filtered and the solvent removed using a vacuum concentrator.

Example 101

1-(4-Bromophenyl)-3-(3-dimethylamino propyl) urea (CFM2134)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (77.2 mg, 0.38 mmol), 4-bromoaniline (30.0 mg, 0.174 mmol) and triethylamine (38.8 mg, 0.38 mmol) to form the intermediate followed by 3-(dimethylamino)propylamine (26.6 mg, 0.26 mmol) to form the desired product. Work-up as in Example 100. The crude product was purified by flash chromatography using MeOH/$CHCl_3$ (40:60).

Example 102

3-(4-Bromophenyl)-1-methyl-1-(3-dimethylamino propyl) urea (CFM2139)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (87.0 mg, 0.436 mmol), 4-bromoaniline (50.0 mg, 0.29 mmol) and triethylamine (44.0 mg, 0.436 mmol) refluxed for 5 hours in anhydrous THF (20mL) to form the intermediate. Then *N,N,N'*-trimethyl-1,3-propanediamine (50.5 mg, 0.436 mmol) was added and

the reaction mixture refluxed for 18 hours to form the title compound. Work-up as in Example 100.

Example 103

1-(3-Phenyl-5-methoxy phenyl)-3-(3-dimethylamino propyl) urea (CFM2148)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (45.5 mg, 0.226 mmol), 5-phenyl-*o*-anisidine (30.0 mg, 0.151 mmol) and triethylamine (22.8 mg, 0.226 mmol) refluxed in anhydrous THF (20 mL) for 18 hours to form the intermediate followed by 3-(dimethylamino)-propylamine (23.1 mg, 0.226 mmol) and refluxed for a further 5 hours to form the title compound. Work-up as in Example 100.

Example 104

3-(4-Chlorophenyl)-1-methyl-1-(3-dimethylamino propyl) urea (CFM2200)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (830 mg, 4.12 mmol), 4-chloroaniline (350 mg, 2.75 mmol) and triethylamine (416 mg, 4.12 mmol) refluxed for 7 hours in anhydrous THF (30mL) to form the intermediate. Then *N,N,N'*-trimethyl-1,3-propanediamine (478 mg, 4.12 mmol) was added and the reaction mixture refluxed for 18 hours to form the title compound. Work-up as in Example 100.

Example 105

1-(3-Nitrophenyl)-1-benzyl-3-(3-dimethylamino propyl) urea (CFM2270)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (66.0 mg, 0.328 mmol), N-benzyl-3-nitroaniline (50.0 mg, 0.219 mmol) and triethylamine (33.0 mg, 0.328 mmol) refluxed in anhydrous THF (20 mL) for 6 hours to form the intermediate followed by 3-(dimethylamino)propylamine (44.6 mg, 0.438 mmol) and refluxed for a further 36 hours to form the title compound. Work-up as in Example 100.

Example 106

1-Benzyl-1-(4-methyl-3-pyridinyl)-3-(3-dimethylamino propyl) urea (CFM2271)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (76.0 mg, 0.378 mmol), 2-benzylamino-4-methyl-pyridine (50.0 mg, 0.25 mmol) and triethylamine (38.0 mg, 0.378 mmol) refluxed in anhydrous THF (20 mL) for 5 hours to form the intermediate followed by 3-(dimethylamino)propylamine (38.0 mg, 0.378 mmol) and refluxed for a further 18 hours to form the desired product. Work-up as in Example 100. The crude product was purified by flash chromatography using a gradient from 10 to 50 % MeOH (in $CHCl_3$) to give the title compound.

Example 107

1-Methyl-1-(3,5-bistrifluoromethylphenyl)-3-(3-dimethylaminopropyl)urea (CFM2311)

Prepared as in Example 100 using 4-nitrophenyl chloroformate (62.0 mg, 0.308 mmol), N-methyl-3,5-bis(trifluoromethyl)aniline (50.0 mg, 0.206 mmol) and triethylamine (31.0 mg, 0.308 mmol) refluxed in anhydrous THF (20 mL) for 5 hours to form the intermediate followed by 3-(dimethylamino)propylamine (31.5 mg, 0.308 mmol) and refluxed for a further 18 hours to form the desired product. Work-up as in Example 100. The crude product was purified by flash chromatography using a gradient from 10 to 40 % MeOH (in $CHCl_3$) to give the title compound.

Example 108

1-(2-Phenacyl-4-chorophenyl)-1-methyl-3-(3-dimethylamino propyl) urea (CFM2310)

4-Nitrophenyl chloroformate (61.5 mg, 0.31 mmol), 5-chloro-2-(methylamino)-benzophenone (50.0 mg, 0.20 mmol) and triethylamine (30.80 mg, 0.31 mmol) were refluxed for 5 hours in anhydrous THF (20 mL) as in Example 100 to form the intermediate. Then 3-(dimethylamino)-propylamine (32.0 mg, 0.31 mmol) was added and the mixture was refluxed for a further 5 hours to form the desired product. Work-up as in Example 100. The crude product was purified by flash chromatography using a gradient from 10 - 40% MeOH (in $CHCl_3$) to give the title compound.

Example 109

1-(2-Chloro-4-trifluoromethylphenyl)-3-(3-dimethylaminopropyl) urea (CFM2421)

4-Nitrophenyl chloroformate (77.0 mg, 0.39 mmol), 4-amino-3-chloro-benzotrifluoride (50.0 mg, 0.26 mmol) and triethylamine (38.0 mg, 0.39 mmol) were refluxed for 18 hours in anhydrous THF (20 mL) as in Example 100 to form the intermediate. Then 3-(dimethylamino)-propylamine (38.0 mg, 0.39 mmol) was added and the mixture was refluxed for a further 5 hours to form the desired product. Work-up as in Example 100. The crude product was purified by flash chromatography using a gradient from 10 - 40% MeOH (in $CHCl_3$) to give the title compound.

Example 110

1-(3-Fluoro-5-trifluoromethylphenyl)-3-(3-dimethylaminopropyl) urea (CFM2422)

4-Nitrophenyl chloroformate (84.0 mg, 4.19 mmol), 3-amino-5-fluorobenzotrifluoride (50.0 mg, 0.28 mmol) and triethylamine (42.0 mg, 4.19 mmol) were refluxed for 18 hours in anhydrous THF (20 mL) as in Example 100 to form the intermediate. Then 3-(dimethylamino)-propylamine (42.0 mg, 4.19 mmol) was added and the mixture was refluxed for a further 5 hours to form the desired product. Work-up as in Example 100. The crude product was purified by flash chromatography using a gradient from 10 - 40% MeOH (in $CHCl_3$) to give the title compound.

Example 111

1-(3-N-*tert*-butoxycarbonyl-benzylamino)-3-(3-dimethylaminopropyl) urea CFM2374

4-Nitrophenyl chloroformate (3.13 g, 15.54 mmol), 3-amino-1-(N-*tert*-butoxy-carbonyl)benzylamine (2.30 g, 10.36 mmol) and triethylamine (1.56 g, 15.54 mmol) was refluxed for 18 hours in anhydrous THF (100 mL) as in Example 100 to form the intermediate. Then 3-(dimethylamino)propylamine (1.58 g, 15.54 mmol) was

added and the mixture was refluxed for a further 5 hours to form the desired product. Work-up same as in Example 100. The crude product was purified by flash chromatography using a gradient from 10 - 40% MeOH (in $CHCl_3$) to give the title compound.

Example 112

N-(3-Dimethylamino-propyl)-2-[1-(4-fluorobenzoyl]-benzamide (CFM2262)

2-(4-Fluorobenzoyl)benzoic acid (1.25 g, 5.12 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (4.30 g, 15.36 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.95 g, 5.12 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.52 g, 5.12 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (3.40 g, 15.36 mmol) was added and the mixture was allowed to stir for 5 hours. To the mixture was added water (5 mL) and the solvent was removed on a vacuum concentrator. The crude product was purified by flash chromatography using a gradient from 5 to 10% MeOH (in $CHCl_3$) and the title compound was isolated as a white solid 0.36 g, 22 % yield (mp 84 - 85 °C).

Example 113

2-[1-(4-Chlorobenzoyl]-N-(3-dimethylamino-propyl)-benzamide (CFM 2269)

2-(4-Chlorobenzoyl)-benzoic acid (1.25 g, 4.80 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (4.00 g, 14.38 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.82 g, 4.80 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.50 g, 4.80 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (3.20 g, 14.40 mmol) was added and the mixture was left to stir for 5 hours. The workup and purification was the same as

described in Example 112. The title compound was isolated as a white solid 0.68g, 41 % yield (mp 108-110 °C).

Example 114

5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2404)

5-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (1.10 g, 4.09 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (3.40g, 12.27 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.56 g, 4.09 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.42 g, 4.09 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (2.70 g, 12.27 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same as described in Example 112. The title compound was isolated as a white solid 0.62g, 44 % yield (mp 165 °C).

Example 115

5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2408)

5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (1.00 g, 3.68 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (3.00 g, 11.04 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.49 g, 3.68 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.38 g, 3.68 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (2.43 g, 11.00 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same

as described in Example 112. The title compound was isolated as a white solid 0.24 g, 18.5 % yield (mp 143-144 °C).

Example 116

N-(3-Dimethylamino-propyl)-2-(2-phenylsulfamoyl-phenylsulfanyl)-benzamide(CFM2349)

2-(2-Phenylsulfamoyl-phenylsulfanyl)-benzoic acid (1.10 g, 2.60 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (2.18g, 7.78 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (0.98 g, 2.6 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.26 g, 2.60 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (1.70 g, 7.78 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same as described in Example 112. The title compound was isolated as a white solid (0.1 g, 9 %), (mp 75-76 °C).

Example 117

2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide (CFM2351)

2-Benzylsulfanyl-benzoic acid (1.00 g, 4.09 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (3.40 g, 12.27 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.55 g, 4.09 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.42 g, 4.09 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (2.60 g, 12.27 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same

as described in Example 112. The title compound was isolated as a white solid 0.41g, 30.5 % yield (mp 85-86 °C).

Example 118

6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2339)

6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (1.00 g, 3.31 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (2.78 g, 9.93 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.25 g, 3.31 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.34 g, 3.31 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (2.18 g, 9.93 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same as described in Example 112. The title compound was isolated as a white solid (0.26g) in 20 % yield (mp 135-136 °C).

Example 119

3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide (CFM2346)

3-(4-Chlorophenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (1.00 g, 2.84 mmol), *N,N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (2.37 g, 8.53 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N,N*-tetramethyluronium hexafluorophosphate (HATU) (1.08g, 2.84 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.3 g, 2.84 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (1.87 g, 8.52 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and

purification was the same as described in Example 112. The title compound was isolated as a white oil/solid 0.3 g, 24 % yield.

Example 120

4-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-nitro-benzamide (CFM2347)

4--(4-Chlorophenoxy)-3-nitro-benzoic acid (1.00 g, 3.40 mmol), *N*, *N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (2.84 g, 10.20 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium hexafluorophosphate (HATU) (1.29 g, 3.40 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.35 g, 3.40 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (2.24 g, 10.20 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same as described in Example 112. The title compound was isolated as a yellow solid (0.6 g) in 46.5% yield (mp 165-167 °C.

Example 121

N-(3-Dimethylamino-propyl)-4-(4-phenyl-thiazol-2-yl)-benzamide (CFM2405)

4-(4-Phenyl-thiazol-2-yl)-benzoic acid (1.38 g, 4.91 mmol), *N*,*N*-(diisopropyl)amino-methylpolystyrene resin (PS-DIEA), (3.84 g, 14.70 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium hexafluorophosphate (HATU) (1.87 g, 4.91 mmol) was stirred in anhydrous acetonitrile (50 mL) at room temperature under nitrogen for 5 minutes. Then 3-(dimethylamino)propylamine (0.50 g, 4.91 mmol) was added and the temperature was taken up to 50 °C and the mixture was left to stir at this temperature for 18 hours. The mixture was allowed to cool and tetrafluorophthalic anhydride (3.24 g, 14.70 mmol) was added and the mixture was allowed to stir for 5 hours. The workup and purification was the same as described in Example 112. The title compound was isolated as a white solid (1.18 g) in 66% yield (mp 204-205 °C).

Example 122

1-(3-Dimethylamino-propyl)-3-(2-phenoxyphenyl)-urea (CFM2260)

2-Phenoxybenzoic acid (1.50 g, 7.00 mmol) was stirred in anhydrous toluene (50 mL) at 50 °C under nitrogen. To this mixture was added triethylamine (0.71 g, 7.00 mmol) and the temperature was increased to 80 °C at which stage diphenylphosphorylazide (DPPA) (1.92 g, 7.00 mmol) was added and the mixture was left to stir at this temperature for 5 hours. After this period 3-(dimethylamino)propylamine (0.71 g, 7.00 mmol) was added and the mixture was left to stir at 80 °C overnight under nitrogen. The solvent was removed on a vacuum concentrator The residue was taken up in chloroform (100 mL) and washed with 1M sodium hydroxide (2 × 50 mL). The organic fraction was washed with saturated sodium chloride solution and then dried (Na_2S0_4). The solvent was removed on a vacuum concentrator. The crude product was purified by flash chromatography using a gradient from 5 to 10% MeOH (in $CHCl_3$) and the title compound was isolated as a white solid (1.00 g) in 46% yield (mp 126- 128 °C).

Example 123

1-[4-(4-Chloro-phenylsulfanyl)-thiophen-3-yl]-3-(3-dimethylamino-propyl)-urea (CFM2356)

4-(4-Chlorophenylsulfanyl)-thiophene-3-carboxylic acid (1.30 g, 4.80 mmol) was stirred in anhydrous toluene (50 mL) at 50 °C under nitrogen. To this mixture was added triethylamine (0.48 g, 4.80 mmol) and the temperature was increased to 80 °C at which stage diphenylphosphorylazide (DPPA) (1.32 g, 4.80 mmol) was added and the mixture was left to stir at this temperature for 5 hours. After this period 3-(dimethylamino)propylamine (0.48 g, 4.80 mmol) was added and the mixture was left to stir at 80 °C overnight under nitrogen. The solvent was removed on a vacuum concentrator. The residue was taken up in chloroform (100 mL) and washed with 1M sodium hydroxide (2 × 50 mL). The organic fraction was washed with saturated sodium chloride solution and then dried (Na_2S0_4). The solvent was removed on a

vacuum concentrator. The crude product was purified by flash chromatography using a gradient from 5 to 10% MeOH (in $CHCl_3$) and the title compound was isolated as a white solid (0.50 g) in 28% yield (mp 125-126 °C).

Example 124

1-(3-Dimethylamino-propyl)-3-(2'-fluoro-biphenyl-4-yl)-urea (CFM2363)

2-Fluoro-biphenyl-4-carboxylic acid (1.00 g, 4.63 mmol) was stirred in anhydrous toluene (50 mL) at 50 °C under nitrogen. To this mixture was added triethylamine (0.47 g, 4.63 mmol) and the temperature was increased to 80 °C at which stage diphenylphosphorylazide (DPPA) (1.27 g, 4.63 mmol) was added and the mixture was left to stir at this temperature for 5 hours. After this period 3-(dimethylamino)propylamine (0.48 g, 4.63 mmol) was added and the mixture was left to stir at 80 °C overnight under nitrogen. The solvent was removed on a vacuum concentrator. The residue was taken up in chloroform (100 mL) and washed with 1M sodium hydroxide (2 × 50 mL). The organic fraction was washed with saturated sodium chloride solution and then dried (Na_2S0_4). The solvent was removed on a vacuum concentrator. The crude product was purified by flash chromatography using a gradient from 5 to 10% MeOH (in $CHCl_3$) and the title compound was isolated as a orange oil (0.50 g) in 34% yield.

Physical data for some of the compounds synthesised in the Examples is given in Table 3.

TABLE 3: Physical Data

Example	^{1}H NMR δ, $CDCl_3$, 300 MHz	MS	mp	yield
101	7.28 (d, 2H, *J* = 8.7 Hz), 7.17 (d, 2H, *J* = 9.0 Hz), 3.22 (q, 2H, *J* = 5.9 Hz), 2.31 (t, 2H, *J* = 6.2 Hz), 2.12 (s, 6H), 1.58 (quintet, 2H, *J* = 6.2 Hz)	(APCI) 302 $[M+2H]^+$		73%
100	7.31 - 7.27 (m, 2H), 7.16 - 7.19 (m, 2H), 3.26 (q, 2H, *J* = 6.0 Hz), 2.52 (t, 2H, *J* = 6.4 Hz), 2.46 - 2.44 (m, 4H), 1.72 - 1.68 (m, 4H), 1.64 (t, 2H, *J* = 6.2 Hz)	(APCI) 328 $[M+2H]^+$		69%
102	CD_3OD 7.37 (d, 2H, *J* = 9.0 Hz), 7.29 (d, 2H, *J* = 8.7 Hz), 3.41 (t, 2H, *J* = 6.4 Hz), 2.95 (s, 3H), 2.37 (t, 2H, *J* = 6.9 Hz), 2.29 (s, 6H), 1.81 (quintet, 2H, *J* = 6.7 Hz)	(FAB) 314 M^+		85%
103	8.31 (d, 1H, *J* = 2.26 Hz), 7.62, (t, 2H, *J* = 7.16 Hz), 7.41 (t, 2H, *J* = 6.41 Hz), 7.33 - 7.29 (m, 1H), 7.25 (dd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz), 6.94 (d, 1H, *J* = 8.67 Hz), 3.92 (s, 3H), 3.40 (q, 2H, *J* = 5.9 Hz), 2.39 (q, 2H, *J* = 6.7 Hz), 2.18 (s, 6H), 1.74 - 1.65 (m, 2H)	(FAB) 328 $[M+1H]^+$		85%
104	9.86 (br s, 1H), 7.26 (d, 2H, *J* = 9.0 Hz), 7.12 (d, 2H, *J* = 9.0 Hz), 3.31 (t, 2H, *J* = 5.8 Hz), 2.83 (s, 3H), 2.32 (t, 2H, *J* = 5.8 Hz), 2.22 (s, 6H), 1.69 (quintet, 2H, *J* = 5.8 Hz)	(FAB) 270 $[M+1H]^+$		31%
105	8.04 - 8.00 (m, 1H), 7.95 - 7.91 (m, 1H), 7.45 - 7.35 (m, 2H), 7.25 - 7.14 (m, 5H), 6.49 (br s, 1H), 4.85 (s, 2H), 3.29 (m, 2H), 2.24 (t, 2H, *J* = 5.7 Hz), 1.81 (s, 6H), 1.54 (q, 2H, *J* = 5.7 Hz)	(EI) 356 M^+		26%
106	acetone-d_6 8.42 (d, 1H, *J* = 4.9 Hz), 7.53 - 7.41 (m, 5H), 7.16 (s, 1H), 7.06 (d, 1H, *J* = 5.3 Hz), 5.48 (s, 2H), 3.68 (m, 2H), 3.04 (brs, 2H), 2.76 (s, 6H), 2.45 (s, 3H), 2.19 (m, 2H)	(APCI) 327 $[M+1H]^+$		37%
108	7.43 (d, 1H, *J* = 2.26 Hz), 7.31 - 7.15 (m, 7H), 6.72 (d, 1H, *J* = 9.05 Hz), 3.76 - 3.69 (m, 1H), 3.32 (s, 3H), 3.33 - 3.30 (m, 1H), 2.60 - 2.40 (m, 2H), 2.19 (brs, 6H), 1.78 - 1.63 (m, 2H)	(APCI) 374 $[M+1H]^+$		30%
107	7.68 (s, 2H), 7.63 (s, 1H), 6.77 (br s, 1H), 3.35 - 3.31 (m, 2H), 3.28 (s, 3H), 2.64 - 2.52 (m, 2H), 2.23 (br s, 6H), 1.80 - 1.68 (m, 2H)	(APCI) 372 $[M+1H]^+$		33%
111	7.47 - 7.43 (m,2H), 7.35 (t, 1H, *J* = 7.9Hz), 7.06 (d, 1H, *J* = 7.53 Hz), 4.38 (d, 2H, *J* = 5.27 Hz), 4.05 - 3.85 (br s, 3H), 3.50 - 3.40 (m, 2H), 2.80 (t, 2H, *J* = 6.6 Hz), 2.56 (s, 6H), 1.92 (t, 2H, *J* = 6.2 Hz), 1.59 (s, 9H)	(FAB) 351 $[M+1H]^+$		83%
109	8.36 (d, 1H, *J* = 8.67 Hz), 7.69 (s, 1H), 7.53 (d, 1H, *J* = 8.29 Hz), 3.08 (t, 2H, *J* = 7.73 Hz), 2.80 (s, 6H), 1.94 (2H, t, *J* = 7.35 Hz), 1.31 (t, 2H, *J* = 7.16 Hz)	(EI) 323 M^+		24%
110	7.56 (br s, 1H), 7.51 (br s, 1H), 6.97 (br d, 1H, *J* = 8.29 Hz), 3.26 (t, 2H, *J* = 6.78 Hz), 2.62 (t, 2H, *J* = 7.73 Hz), 2.44 (s, 6H), 1.79 (t, 2H, *J* = 7.53 Hz)	(FAB) 308 $[M+1H]^+$		35%

112	7.81 (d, 1H, J = 6.41 Hz), 7.64 - 7.52 (m, 2H), 7.48 - 7.39 (m, 2H), 7.29 (d, 1H, J = 6.78 Hz), 7.10 (t, 2H, J = 8.86 Hz), 3.65 - 3.56 (m, 1H), 3.21 - 3.11(m, 1H), 2.92 (t, 2H, J = 7.54 Hz), 2.69(s, 6H), 1.93 - 1.76 (m, 2H)	EI 328 $[M]^+$	84-85°C	44%
113	7.81 (d, 1H, J = 6.78 Hz), 7.63 - 7.52 (m, 2H), 7.38 (s, 4H), 7.29 (d, 1H, J = 6.78 Hz), 3.65 - 3.56 (quintet, 1H, J = 7.06 Hz), 3.20 - 3.10 (quintet, 1H, J = 7.06 Hz), 2.92 (t, 2H, J = 7.35 Hz), 2.68 (s, 6H), 1.93 - 1.77 (m, 2H)	(APCI) 345 $[M]^+$	108-110°C	41%
114	7.45 - 7.43 (m, 3H), 7.37 - 7.32 (m, 3H), 7.23 (d, 2H, J = 8.67, Hz), 7.02 (s, 1H), 3.50 (t, 2H, J = 6.40 Hz), 3.20 (t, 2H, J = 7.73, Hz), 2.91 (s, 6H), 2.08 - 1.99 (quintet, 2H, J = 7.25 Hz)	(APCI) 383 M^+	165°C	44%
115	7.57 - 7.38 (m, 7H), 7.22 (dd, 1H, J = 8.67 Hz, J = 1.89 Hz), 3.29 (t, 2H, J = 6.78 Hz), 2.19 (t, 2H, J = 7.53 Hz), 2.16 (s, 6H), 1.60 (quintet, 2H, J = 7.25 Hz)	(FAB) 356 $[M]^+$	143-144°C	18.5 %
116	8.02 (dd, 1H, J = 7.73 Hz, J = 1.7 Hz), 7.50 (dd, 1H, J = 7.54 Hz, J = 1.51 Hz), 7.41 - 7.11 (m, 9H), 7.01 (t, 2H, J = 6.97 Hz), 3.36 (t, 2H, J = 6.78 Hz), 2.42 (t, 2H, J = 7.91 Hz), 2.21 (s, 6H), 1.74 (quintet, 2H, J = 7.25 Hz)	(APCI) 470 $[M]^+$	75-76°C	9%
117	7.43 - 7.20 (m, 9H), 4.16 (s, 2H), 3.36 (t, 2H, J = 6.78 Hz), 2.45 (t, 2H, J = 7.73 Hz), 2.23 (s, 6H), 1.79 (quintet, 2H, J = 7.35 Hz)	(APCI) 329 M^+	85-86°C	30.5 %
118	8.05 (d, 1H, J = 2.64 Hz), 7.89 (d, 1H, J = 2.26 Hz), 7.88 (s, 1H), 3.47 (t, 2H, J = 6.78 Hz), 2.44 (t, 2H, J = 7.72 Hz), 2.27 (s, 6H), 1.84 (quintet, 2H, J = 7.34 Hz), 1.57 (s, 9H), 1.39 (s, 9H)	(APCI) 387 $[M]^+$	135-136°C	20%
119	7.54 (d, 2H, J = 8.66 Hz), 7.45 (d, 2H, J = 8.67 Hz), 3.20 (t, 2H, J = 6.79 Hz), 3.07 (d, 2H, J = 7.15 Hz), 2.17 (s, 3H), 2.14 (t, 2H, J = 7.92 Hz), 2.05 - 1.92 (m, 1H), 1.56 (quintet, 2H, J = 7.44 Hz), 1.09 (d, 6H, J = 6.78 Hz)	(APCI) 436 $[M]^+$		24%
120	($CDCl_3$) 8.50 (d, 1H, J = 2.26 Hz), 8.08 (dd, J = 8.66 Hz, J = 2.26 Hz), 7.31 (d, 2H, J = 9.04 Hz), 6.96 (d, 2H, J = 8.66 Hz), 6.91 (s, 1H), 3.56 (q, 2H, J = 5.91 Hz), 3.07 (t, 2H, J = 6.60 Hz), 2.79 (s, 6H), 2.11 (quintet, 2H, J = 6.03 Hz)	(APCI) 378 $[M]^+$	mp 165-167°C	46.5 %
121	8.16 (d, 2H, J = 8.67 Hz), 8.04 (d, 2H, J = 7.16 Hz), 7.97 (d, 2H, J = 8.67 Hz), 7.90 (s, 1H), 7.46 (t, 2H, J = 7.35 Hz), 7.37 (d, 1H, J = 7.53 Hz), 3.50 (t, 2H, J = 6.78 Hz), 3.03 (t, 2H, J = 7.54 Hz), 2,77 (s, 6H), 2.00 (quintet, 2H, J = 7.07 Hz)	(APCI) 366 [M]	mp 204-205°C	66%
122	8.06 (dd, 1H, J = 8.11 Hz, J = 1.7 Hz), 7.34 (t, 2H, J = 8.11 Hz), 7.12 - 7.05 (m, 2H), 6.98 - 6.91 (m, 3H), 6.82 (dd, 1H, J = 8.29 Hz, J = 1.51 Hz), 3.19 (t, 2H, J = 6.78 Hz), 2.26 (s, 6H), 1.73 - 1.63 (quintet, 2H, J = 7.25 Hz)	(FAB) 314 $(M + H)^+$	mp 126-128°C	44%

123	7.72 (d, 2H, J = 3.39 Hz), 7.57 (d, 2H, J = 3.76 Hz), 7.24 (d, 2H, J = 8.66 Hz), 6.99 (d, 2H, J = 8.67 Hz), 3.16 (t, 2H, J = 6.59 Hz), 2.32 (t, 2H, J = 7.72 Hz), 2.22 (s, 6H), 1.64 (quintet, 2H, J = 7.25 Hz)	(FAB) 370 M^+	mp 125-126°C	28%
124	7.44 (bs, 4H), 7.31 - 7.11 (m, 4H), 3.25 (t, 2H, J = 6.78 Hz), 2.44 (t, 2H, J = 7.72 Hz), 2.29 (s, 6H), 1.79 - 1.69 (quintet, 2H, J = 7.25 Hz)	(APCI) 316 $[M+1H]^+$		35-4%

Activity Example 1

Compounds of the invention were assayed to determine their ability to activate sGC. The assay employed was an enzyme immunoassay to measure changes in cGMP. To perform the assay recombinant soluble Guanylate cyclase was added to 1.1 mg/ml IBMX, 2.6 mg/ml GTP, 667 nM DeaNO and the test compound (10μM). The mixture was then incubated at room temperature for 10 minutes. Compounds were formulated in DMSO diluted in Tris HCl (pH 7.4) buffer and with a final DMSO concentration of <0.5%.

To determine the amount of cGMP produced, the Biotrak™ cGMP enzyme immunoassay system commercially available from Amersham™ was used.

The assay is based on the competition between unlabelled cGMP and a fixed quantity of peroxidase labelled cGMP for a limited amount of cGMP specific antibody. The peroxidase ligand that is bound to the antibody is immobilised on precoated microtitre wells. The amount of labelled cGMP is determind using a one pot stabilised substrate. The concentration of unlabelled cGMP in a sample is determined by interpolation from a standard curve.

The results are shown in Tables 4 to 7. The results shown in Tables 6 and 7 relate to commercially available compounds.

Activity Example 2

The ability of the compounds of the invention to inhibit platelet aggregation was also determined. IC_{50} values were measured as set out below.

Materials

Prostacyclin (PGI_2 ; ICN Pharmaceuticals, Oxford) in Tris (0.05M, pH 9), Sodium citrate solution, Tyrodes solution without calcium (140mM NaCl; 3mM KCl; 12mM $NaHCO_3$; 0.4mM $NaH_2PO_4.H_2O$; 2mM $MgCl_2.6H_2O$; 0.1% Glucose) contains 0.05M Hepes, pH7.4. Collagen (collagenreagent Horm, Nycomed Arzneimittel GmbH, Munchen).

PGI_2 dissolved in Tris buffer (0.05M, pH9). Test compounds dissolved in DMSO (at 10mM) and subsequent dilutions made in Tyrodes; final assay concentration of DMSO did not exceed 0.1% (which is without effect on platelet reactivity).

Platelet Preparation

Platelets prepared according to Vagas, J.R., Radomski, M. and Moncada, S. *The use of prostacyclin in the separation from plasma and washing of human platelets.* PROSTAGLANDINS 1982; 23:6:929-945.

Briefly, fresh human blood was collected into tubes containing 1:9 sodium citrate (3.15%) and centrifuged immediately at 260g for 20 minutes to separate the red cells from the platelet rich plasma (PRP). The PRP was decanted and PGI_2 (0.3µg/ml) was added. The PRP was then centrifuged at 180g for 10mins to sediment the remaining red and white cells. The resulting PRP was decanted into new tubes, PGI_2 (0.15µg/ml) added and centrifuged at 950 g for 10 mins to sediment the platelets. The resultant platelet poor plasma (PPP) was discarded and the platelet pellet was resuspended in an equal volume of Tyrodes buffer by gently pipetting up and down. The suspension was centrifuged at 870 g for 10mins at 4 °C. The supernatant was discarded and the platelet pellet was resuspended in an equal volume of Tyrodes buffer as before. The platelets were counted (using a Coulter Counter model T540 (address)) and normalised to 250,000cells/µl using Tyrodes. The resultant suspension was placed on ice for approximately 1 hour until use.

Platelet Assays

Platelet aggregation was monitored using either a Chrono-Log model 560-CA dual channel ormodel 570-4S four channel aggregometer (Chrono-Log Corp., Havertown, PA). Aggregation was analysed by using 0.5 mL aliquots of the platelet suspension at 37 °C using % light transmittance.

For each sample, baseline reading was established for a 3 min period, followed by addition of test compound or buffer. An EC_{50} dose of collagen was added 1 min later and the response measured 3 min after addition of collagen.

Data Analysis

The amplitude of each aggregatory response, normalised to the collagen control, was used to plot dose-response curves. The concentration of drug that inhibited collagen-induced platelet aggregation by 50% (IC_{50}) was calculated from the dose-response curves.

The results are shown in Tables 4 to 7. The results shown in Tables 6 and 7 relate to commercially available compounds.

Table 4

Example	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
70	153.79	4
71	136.37	10+
72	135.49	
73	143.35	
74	158.0	
75	163.88	10+
76	303.25	6
77	284.9	8
78	303.77	4
79	218.24	10+
80	244.87	6.5
81	230.49	4.5
82	224.57	
83	314.64	6
84	408.17	3.5
85	358.65	2
86	358.65	10+
87	336.16	10+
88	377.13	10+
89		10+
90		6
91		2.5
92		5
93		4
94		10+
95		10+
96		10+
97		9.5
98		10+
99		5
101	199.21	
100	135.7	
102	273.17	
103		8

Example	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
104		10
105	181.53	
106	137.91	
108	129.29	
107	125.26	
111	476.39	10+
109		7
110		10+

Table 5

Example	1st Test cGMP Change with 1mM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
1	93.33	3.5
2	145.84	6
3	132.77	10+
4	184.86	7
5	134.99	5
6	131.66	8
7	178.03	
8	125.15	2
12	128.76	
13	169.14	
14	166.45	
9	153.88	10+
10	157.53	6
11	174.75	6
15	201.95	6
16	282.88	6.5
17	173.64	6
18	201.95	10+
19	209.14	10+
20	459.96	5
21	250.98	10+
22	186.32	
23	225.46	
24	249.76	
25	142.96	
26	299.44	1.5
27	338.6	6
28	144.71	
29	256.76	3.5
30	201.33	
31	353.4	1.5

Example	1st Test cGMP Change with 1mM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
32	151.68	10+
34	322.81	6
35	363.36	10+
36	296.59	10+
37	337.89	10+
38	295.16	10+
39	312.4	10+
40	418.37	10+
41	455.13	10+
42	181.88	8
43	215.41	10+
44	457.39	10+
45	218.66	5
46		10+
47		10+
48		10+
49		10+
50		10+
52		10+
53		9
54		5
55		7
56		6.5
57		3
58		3
59		10+
60		7.5
61		1.5
62		7
63		9.5
64		10+
65		10+
33		7

Table 6

Compound	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
1-(4-chlorobenzyl)-3-(2-N,N-dimethylethylamido)-6-pyridone (CFM1882)	156.75	
1-(2,6-dichlorobenzyl)-3-(3-N,N-dimethylpropylamido)-6-pyridone (CFM1883)	421.09	20
1-(3-trifluoromethylbenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone (CFM1884)	207.03	
1-(2,6-dichlorobenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone (CFM1885)	194.38	
1-(3,4-dichlorobenzyl)-3-(N-[2,N,N-dimethylaminoethylamido])-2-pyridone (CFM1886)	204.61	
1-(2,6-dichlorobenzyl)-3-(N-[2-N,N-dimethylaminoethylamido])-6-pyridone (CFM1887)	154.78	
5-chloro-1-(3,4-dichlorobenzyl)-3-(2-N,N-dimethylaminoethylamido)-6-pyridone (CFM1888)	140.94	
5-chloro-3-(2-N,N-dimethylaminoethylamido)-1-(3-trifluoromethylbenzyl)-6-pyridone (CFM1889)	135.6	
5-chloro-1-(3,4-dichlorobenzyl)-3-N-(2-[N',N'-dimethylaminoethylamido])-2-pyridone (CFM1890)	202.02	
5-chloro-1-(4-chlorobenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl)amido-2-pyridone (CFM1891)	170.53	
5-chloro-1-(3-trifluoromethylbenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl)amido-2-pyridone (CFM1892)	164.85	

Compound	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
1-benzyl-5-chloro-3-N-(2-[N',N'-dimethylamino] ethyl)carboxamido-6-pyridone (CFM1893)	148.43	
5-chloro-1-(4-chlorobenzyl)-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido-6-pyridone (CFM1894)	144.32	
4-(2,4-dichlorobenzoyl)pyrrole-2-N-dimethylaminopropylcarboxamide (CFM1985)	360.01	
4-[(N-[3-(N',N'-dimethylaminopropyl)] carboxamido]-2-phenylthiazole (CFM1896)	334.25	10
4-(N-(3-N',N'-dimethylaminopropyl) carboxamido)-2-(4-pyridinyl)thiazole (CFM1897)	296.23	
2-[4-(N-[3-N',N'-dimethylaminopropyl] carboxamido)phenyl-4-(3-trifluoromethylphenyl] thiazole (CF1898)	269.18	1.5
4-(4-chlorophenyl)-2-(4-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl)	233.13	1.5
1-(3,5-bis(trifluoromethyl)benzyl)-3-[N-(2-dimethylaminoethyl)carboxamido]-2[1H]-pyridone (CFM1900)	149.33	
N-(3-dimethylaminopropyl)-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenylsulfonamide (CFM1901)	191.9	
N1-[3-(dimethylamino)propyl]-3-[3-chloro-5-(trifluoromethyl)-2-pyridyl]propanamide (CFM1902)	309.73	
3-(N-(2-dimethylaminoethyl)carboxamido]-1-(4-trifluoromethylbenzyl))-2[1H]-pyridone (CFM1905)	169.35	
1-ethyl-3-(3-dimethylaminopropyl)urea (CFM1917)	266.6	

Compound	1st Test cGMP Change with 1μM cpd (NO Donor Present), % of DEANO response	IC_{50} for Inhibition of Platelet Aggregation (μM)
1-(3-(dimethylamino)-propyl)-3-phenylurea (CFM1918)	281.16	
N1-[2-(2,4-dichlorophenoxy)phenyl]-N2-[3-(dimethylamino)propyl]ethanediamide (CFM1935)	207.01	
N4-[3-(dimethylamino)propyl]-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide (CFM1936)	142.14	
N-[[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]carbonyl]-N'-[3-(dimethylamino)propyl]urea (CFM1937)	334.47	
N-(4-chlorophenyl)-N'-[3-dimethylaminopropyl] urea (CFM1938)	299.26	

Table 7

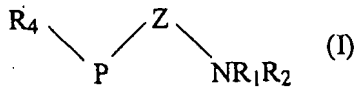
Compound	1st Test cGMP Change with 1mM cpd (NO Donor Present), % of DEANO response
N-(3,5-Dichloro-phenyl)-3-(3-dimethylamino-propylamino)propionamide	174.42
[3-(2-Ethyl-6-methyl-pyridin-3-yloxy)-propyl]-dimethyl-amine	188.03
8-(3-Dimethylamino-propoxy)-1,3,7-trimethyl-3,7-dihydro-purine-2,6-dione	191.65
2-(3-Dimethylamino-propylamino)-isophthalonitrile	213.04
Dimethylamino-(3-methyl-benzo[b]thiophen-2-yl)-propan-1-one (HCl)	279.33
N-Benzo[1,3]dioxol-5-ylmethyl-N,N-dimethyl-propane-1,3-diamine	184.90
N,N-Dimethyl-N-(5-nitro-quinolin-8-yl)-propane-1,3-diamine	219.03
1-(4-Chloro-phenyl)-3-(3-dimethylamino-propyl)-urea	421.21
2-Amino-N-(3-dimethylamino-propyl)-benzamide	363.98
3-Phenyl-acrylic acid 3-dimethylamino-propyl ester	298.89
3,5-Dinitro-benzoic acid 2-dimethylamino-ethyl ester	141.22
[4-(4-Bromo-phenyl)-3-(3-dimethylamino-propyl)-3H-thiazol-2-ylidene]-phenyl-amine	204.10
3-Methyl-benzofuran-2-carboxylic acid dimethylamino-dimethyl-propyl ester	197.46

N'-(2-Chloro-4-nitro-phenyl)-N,N-dimethyl-propane-1,3 -diamine	161.70
[3-(3-Dimethylamino-propyl)-5-(4-nitro-phenyl)-3H-thiazol -2-ylidene]-phenyl-amine	157.02
[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene) -propyl]-dimethyl-amine	150.39
2,3-Dimethyl-1H-indole-5-carboxylic acid 2-dimethylamino -ethyl ester	217.3
N'-(3,4-Dinitro-5-pyridin-2-yl-thiophen-2-yl)-N,N-dimethyl -propane-1,3-diamine	282.12
Cyclooctyl-dithiocarbamic acid 2-dimethylamino-ethyl ester (HCl)	185.31
N-(2,6-Difluoro-phenyl)-C-dimethylamino-acetamide	168.99
2-Acetylamino-3-(4-chloro-phenyl)-N-(3-dimethylamino -propyl)-acrylamide	142.31
N-[2-[5-(4-Bromo-phenyl)-furan-2-yl]-1-(3-dimethylamino -propylcarbamoyl)-vinyl]-4-methyl-benzamide	163.49
2,6-Bis-(3-dimethylamino-propylamino)-3-nitro-benzonitrile	167.75
N-[2-(2,4-Dichloro-phenoxy)-phenyl]-N'-(3-dimethylamino -propyl)-oxalamide	328.31
3,5-Dichloro-N-(3-dimethylamino-propyl)-2,6-dimethoxy -benzamide	193.93
2-Dimethylaminomethyl-3,4-dihydro-2H-naphthalen-1 -one (HCl)	175.73
2-({1-[N-(3-Dimethylamino-propyl)-3-trifluoromethyl -phenyl]-methanimidoyl}-amino)-6-fluoro-benzoic acid	231.40

2,4-Dichloro-N-(3-dimethylamino-propyl)-N'-hydroxy -benzamidine	212.83
3-(3-Methyl-ureido)-4-oxo-3,4-dihydro-quinazoline-2 -carboxylic acid (3-dimethylamino-propyl)-amide	305.22
5-Bromo-N-(3-dimethylamino-propyl)-2-hydroxy-benzamide	258.28
N-(2,4-Dichloro-phenyl)-6-(2-dimethylamino-ethylsulfanyl) -4-trifluoromethyl-nicotinamide	162.85
1-(2,6-Dichloro-benzyl)-2-oxo-1,2-dihydro-pyridine-3 -carboxylic acid (2-dimethylamino-ethyl)-amide	149.44
3-Amino-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide	230.76

CLAIMS

1. Use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the activation of soluble guanylate cyclase



(I)

wherein:

- R_1 and R_2 are the same or different and each represent a C_1-C_6 alkyl group, or R_1 and R_2 together form a C_3-C_6 alkylene group;
- Z is a C_1-C_4 alkylene group;
- P is a direct bond or a moiety -X-, -Y-, -W-, -XY-, -YW- or -XYW-, wherein:
  - W is -O-, -S-, or -NR_3, wherein R_3 is hydrogen or C_1-C_6 alkyl;
  - Y is a moiety -U-V- wherein V is a direct bond or a C_1-C_6 alkylene group and U is -CS-, -CO-, -$S(O)_2$- or -C(=NR)- wherein R is hydrogen, hydroxy or C_1-C_6 alkyl;
  - X is -O- or -NR_6- wherein R_6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl or heteroaryl; and
- R_4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, a group -R-A wherein R is -(C_1-C_6 alkyl)-, -(C_2-C_6 alkenyl)- or -(C_2-C_6 alkynyl)- and A is aryl, heteroaryl, carbocycyl or heterocyclyl, or R_4 is a group -COR'', -CO_2R'', -$S(O)_2R''$ or -$CONR'R''$ wherein R' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl and R'' is is aryl, heteroaryl, carbocyclyl or heterocyclyl.

2. Use according to claim 1, wherein R_1 and/or R_2 are methyl.

3. Use according to claim 1 or 2, wherein Z is propylene.

4. Use according to any one of the preceding claims, wherein P is -XYW- or -YW-.

5. Use according to any one of the preceding claims, wherein W is -O- or -NR_3- wherein R_3 is as defined in claim 1.

6. Use according to any one of the preceding claims, wherein Y is -CO-.

7. Use according to any one of the preceding claims wherein X is -NH-.

8. Use according to any one of the preceding claims wherein R_4 is C_1-C_6 alkyl, aryl, heteroaryl, carbocyclyl, heterocyclyl, -(C_1-C_6 alkyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl or -COR'', -CO_2R'' or -$CONR'R''$ wherein R' is hydrogen or C_1-C_6 alkyl and R'' is an aryl, heteroaryl, carbocyclyl or heterocyclyl group.

9. Use according to any one of the preceding claims, wherein P is -XYW-, X is -NH- and R_4 is phenyl, thienyl or pyrazolyl.

10. Use according to any one of claims 1 to 8, wherein P is -YW- and R_4 is a chromonyl, pyrazolyl, thienyl, phenyl or indolyl group.

11. Use according to claim 1, wherein the compound of formula (I) is
1-(3-Dimethylamino-propyl)-3-(2-phenoxy-phenyl)-urea
1-[2-(4-Chloro-phenoxy)-pyridin-3-yl]-3-(3-dimethylaminopropyl)-urea
1-(3-Dimethylamino-propyl)-3-pyren-1-ylmethyl-urea
1-(3-Dimethylamino-propyl)-3-[(1R,2R)-5-phenyl-2-(1-phenyl-methanoyl)-cyclohexyl]-urea

1-(3-Dimethylamino-propyl)-3-[2-(4-phenoxy-phenyl)-ethyl]-urea

1-(3-Dimethylamino-propyl)-3-[3-methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-1-(4-trifluoromethoxy-phenyl)-1H-pyrazol-4-yl]-urea

2'-[3-(3-Dimethylamino-propyl)-ureido]-biphenyl-2-carboxylic acid (4-fluoro-phenyl)-amide

N-(3-Chloro-4-methyl-phenyl)-4-[3-(3-dimethylamino-propyl)-ureido]-3-phenyl-butyramide

1-[4-(4-Chloro-phenylsulfanyl)-thiophen-3-yl]-3-(3-dimethylamino-propyl)-urea

1-[2-(3,4-Dimethoxy-phenyl)-6-methyl-quinolin-4-yl]-3-(4-dimethylamino-propyl)-urea

1-(6-Bromo-2-thiophen-3-yl-quinolin-4-yl)-3-(3-dimethylamino-propyl)-urea

1-[3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea

1-[6-(2,4-Dichloro-phenyl)-cyclohex-3-enyl]-3-(3-dimethylamino-propyl)-urea

1-(2-Benzylsulfanyl-phenyl)-3-(3-dimethylamino-propyl)-urea

2-{2-[3-(3-Dimethylamino-propyl)-ureido]-phenylsulfanyl}-N-phenyl-benzenesulfonamide

1-(3-Dimethylamino-propyl)-3-(2'-fluoro-biphenyl-4-yl)-urea

N-(3,5-Dichloro-phenyl)-2-{3-[3-(3-dimethylamino-propyl)-ureido]-pyridin-2-ylsulfanyl}-acetamide

1-(3-Dimethylamino-propyl)-3-{2-[1-(1-trifluoromethyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-methanoyl]-phenyl}-urea

8-{2-[3-(3-Dimethylamino-propyl)-ureido]-phenylsulfanyl}-naphthalene-1-carboxylic acid methylamide

1-[1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridin-3-yl]-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-(3-oxo-1,2,3-triphenyl-propyl)-urea

1-[5-(4-Chloro-phenyl)-1-(3,4-dichloro-phenyl)-1*H*-pyrazol-3-yl]-3-(3-dimethylamino-propyl)-urea

1-{4-[4-(4-Chloro-phenyl)-thiazol-2-yl]-phenyl}-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-[5-(4-fluoro-phenyl)-thiophen-2-yl]-urea

1-[3-(4-*tert*-Butyl-benzyloxy)-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-[4-(4-phenyl-thiazol-2-yl)-phenyl]-urea

1-[3-(3,4-Dichloro-benzylsulfanyl)-thiophen-2-yl]-3-(3-dimethylamino-propyl)-urea

1-[2-(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-ylmethylsulfanyl)-phenyl]-3-(3-dimethylamino-propyl)-urea

1-[2-(4-Chloro-benzylsulfanyl)-3-methyl-4-oxo-3,4-dihydro-quinazolin-7-yl]-3-(3-dimethylamino-propyl)-urea

1-(3-Dimethylamino-propyl)-3-{4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-phenyl}-urea

1-(4-Bromophenyl)-3-(3-(1-pyrrolidinyl) propyl) urea

1-(4-Bromophenyl)-3-(3-dimethylamino propyl) urea

3-(4-Bromophenyl)-1-methyl-1-(3-dimethylamino propyl) urea

1-(3-Phenyl-5-methoxy phenyl)-3-(3-dimethylamino propyl) urea

3-(4-Chlorophenyl)-1-methyl-1-(3-dimethylamino propyl) urea

1-(3-Nitrophenyl)-1-benzyl-3-(3-dimethylamino propyl) urea

1-Benzyl-1-(4-methyl-3-pyridinyl)-3-(3-dimethylamino propyl) urea

1-Methyl-1-(3,5-bistrifluoromethylphenyl)-3-(3-dimethylaminopropyl)urea

1-(2-Phenacyl-4-chorophenyl)-1-methyl-3-(3-dimethylamino propyl) urea

1-(2-Chloro-4-trifluoromethylphenyl)-3-(3-dimethylaminopropyl) urea

1-(3-Fluoro-5-trifluoromethylphenyl)-3-(3-dimethylaminopropyl) urea

1-(3-N-*tert*-butoxycarbonyl-benzylamino)-3-(3-dimethylaminopropyl) urea

N-(3-Dimethylamino-propyl)-2-[1-(4-fluorobenzoyl]-benzamide

2-[1-(4-Chlorobenzoyl]-N-(3-dimethylamino-propyl)-benzamide

5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-(2-phenylsulfamoyl-phenylsulfanyl)-benzamide

2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide

6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (3-dimethylamino -propyl)-amide

3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-nitro-benzamide

N-(3-Dimethylamino-propyl)-4-(4-phenyl-thiazol-2-yl)-benzamide

1-(3-Dimethylamino-propyl)-3-(2-phenoxyphenyl)-urea

1-[4-(4-Chloro-phenylsulfanyl)-thiophen-3-yl]-3-(3-dimethylamino-propyl) -urea

1-(3-Dimethylamino-propyl)-3-(2'-fluoro-biphenyl-4-yl)-urea

N-(3-Dimethylamino-propyl)-2-[1-(4-fluorobenzoyl]-benzamide

N-(3-Dimethylamino-propyl)-3-phenoxy-benzamide

N-(3-Dimethylamino-propyl)-2-phenoxy-benzamide

2-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-nicotinamide

4'-n-Propyl-biphenyl-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-[1-(4-Bromo-phenyl)-methanoyl]-cyclohexanecarboxylic acid (3-dimethylamino-propyl)-amide

5-(3-Trifluoromethyl-phenyl)-furan-2-carboxylic acid (3-dimethylamino-propyl)-amide

2-[1-(4-Chlorobenzoyl]-N-(3-dimethylamino-propyl)-benzamide

2-Phenyl-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-[1-(4-Chloro-3-nitrobenzoyl)]-N-(3-dimethylamino-propyl)-benzamide

N-(3-Dimethylamino-propyl)-2-pyren-1-yl-acetamide

N-(3-Dimethylamino-propyl)-2-[1-(3-methyl-benzo[b]thiophen-2-yl)-methanoyl]-benzamide

4-Chloro-N-(3-dimethylamino-propyl)-2-phenoxy-benzamide

N-(3-Dimethylamino-propyl)-3-(4-phenoxy-phenyl)-propionamide

N-(3-Dimethylamino-propyl)-2-[1-(1-trifluoromethyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-methanoyl]-benzamide

1-(4-Chloro-phenyl)-2,5-dimethyl-1-pyrrole-3-carboxylic acid (3-dimethylamino-propyl)-amide

2-{1-[(3-Dimethylamino-propylcarbamoyl)-methyl]-cyclopentyl}-N-(4-trifluoromethoxy-phenyl)-acetamide

8-[2-(3-Dimethylamino-propylcarbamoyl)-phenylsulfanyl]-naphthalene-1-carboxylic acid methylamide

3-Methyl-5-(4-methyl-[1,2,3]thiadiazol-5-yl)-1-(4-trifluoromethoxy-phenyl)-1*H*-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

6,8-Di-*tert*-butyl-4-oxo-4*H*-chromene-2-carboxylic acid (3-dimethylamino-propyl)-amide

2-(Furan-2-yl)-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

Biphenyl-2,2′-dicarboxylic acid 2′-[(3-dimethylamino-propyl)-amide]-2-[(4-fluoro-phenyl)-amide]

3-Phenyl-pentanedioic acid (3-chloro-4-methyl-phenyl)-amide (3-dimethylamino-propyl)-amide

2-(3,4-Dimethoxy-phenyl)-6-methyl-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

6-Bromo-(2-thiophen-3-yl)-quinoline-4-carboxylic acid (3-dimethylamino-propyl)-amide

3-(4-Chloro-phenyl)-4-cyano-5-isobutylsulfanyl-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-(4-Chloro-phenoxy)-N-(3-dimethylamino-propyl)-3-nitro-benzamide

6-(2,4-Dichloro-phenyl)-cyclohex-3-ene carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-(2-phenylsulfamoyl-phenylsulfanyl)-benzamide

2'-Fluoro-[1,1'-biphenyl]-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide

Pyrazine-2,3-dicarboxylic acid 2-[(3-dimethylamino-propyl)-amide] 3-[(5,6,7,8-tetrahydro-naphthalen-1-yl)-amide]

2-[(3,5-Dichloro-phenylcarbamoyl)-methylsulfanyl]-N-(3-dimethylamino-propyl)-nicotinamide

2-(3-Trifluoromethyl-phenyl)-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(4-Chloro-phenyl)-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-1-(2,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

1-(2,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-1-(3,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

1-(3,4-Dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-1-(2,6-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

1,1-Dimethyl-indan-4-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-[1-(4-ethyl-phenyl)-methanoyl]-benzamide

N-(3-Dimethylamino-propyl)-3-(2,4,5-trimethyl-phenyl)-butyramide

2-[3-(3,4-Dichloro-phenyl)-ureido]-N-(3-dimethylamino-propyl)-benzamide

N-(3-Dimethylamino-propyl)-4-oxo-2,3,4-triphenyl-butyramide

5-(4-Chloro-phenylsulfanyl)-[1,2,3]thiadiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(3-Chloro-5-trifluoromethyl-pyridin-2-ylsulfanyl)-3-methyl-3*H*-imidazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(2-Chloro-4-trifluoromethyl-phenyl)-[1,3]-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(2,3-Dihydro-1-benzofuran-5-yl)-1,3-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

2-(2,3-Dichloro-phenyl)-1,3-thiazole-4-carboxylic acid (3-dimethylamino-propyl)-amide

4-[4-(4-Chloro-phenyl)-thiazol-2-yl]-N-(3-dimethylamino-propyl)-benzamide

5-(4-Fluoro-phenyl)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-Methyl-2-(3-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (3-dimethylamino-propyl)-amide

3-(4-*tert*-Butyl-benzyloxy)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

4-Oxo-3-(3-trifluoromethyl-phenyl)-3,4-dihydro-phthalazine-1-carboxylic acid (3-dimethylamino-propyl)-amide

2-(4-Chloro-phenyl)-N-(3-dimethylamino-propyl)-4-oxo-4-phenyl-butyramide

5-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-4-(4-phenyl-thiazol-2-yl)-benzamide

1-(2,4,5-Trichloro-phenylsulfonyl)-pyrrolidine-2-carboxylic acid (3-dimethylamino-propyl)-amide

3-(3,4-Dichloro-benzylsulfanyl)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

5-Chloro-3-phenyl-1*H*-indole-2-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-[1-(4-fluoro-benzyl)-1*H*-indol-3-yl]-acetamide

2-Phenyl-imidazo[1,2-a]pyridine-3-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-2-(7-ethyl-1*H*-indol-3-yl)-4-oxo-4-phenyl-butyramide

Phenyl-trifluoromethyl-thieno[3,2-b]pyridine-2-carboxylic acid (3-dimethylamino-propyl)-amide

3-(4-Nitro-3-trifluoromethyl-phenoxy)-thiophene-2-carboxylic acid (3-dimethylamino-propyl)-amide

2-(5-Chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-ylmethylsulfanyl)-N-(3-dimethylamino-propyl)-benzamide

2-(4-Chloro-benzylsulfanyl)-3-methyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic acid (3-dimethylamino-propyl)-amide

N-(3-Dimethylamino-propyl)-4-[4-(4-methoxy-phenyl)-pyrimidin-2-ylsulfanylmethyl]-benzamide

1-(4-chlorobenzyl)-3-(2-N,N-dimethylethylamido)-6-pyridone

1-(2,6-dichlorobenzyl)-3-(3-N,N-dimethylpropylamido)-6-pyridone

1-(3-trifluoromethylbenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone

1-(2,6-dichlorobenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone

1-(3,4-dichlorobenzyl)-3-(N-[2,N,N-dimethylaminoethylamido])-2-pyridone

1-(2,6-dichlorobenzyl)-3-(N-[2-N,N-dimethylaminoethylamido])-6-pyridone

5-chloro-1-(3,4-dichlorobenzyl)-3-(2-N,N-dimethylaminoethylamido)-6-pyridone

5-chloro-3-(2-N,N-dimethylaminoethylamido)-1-(3-trifluoromethylbenzyl)-6-pyridone

5-chloro-1-(3,4-dichlorobenzyl)-3-N-(2-[N',N'-dimethylaminoethylamido])-2-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl)amido-2-pyridone

5-chloro-1-(3-trifluoromethylbenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl) amido-2-pyridone

1-benzyl-5-chloro-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido-6-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido -6-pyridone

4-(2,4-dichlorobenzoyl)pyrrole-2-N-dimethylaminopropylcarboxamide

4-[(N-[3-(N',N'-dimethylaminopropyl)]carboxamido]-2-phenylthiazole

4-(N-(3-N',N'-dimethylaminopropyl)carboxamido)-2-(4-pyridinyl)thiazole

2-[4-(N-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl-4-(3-trifluoromethylphenyl)]thiazole

4-(4-chlorophenyl)-2-(4-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl) thiazole

1-(3,5-bis(trifluoromethyl)benzyl)-3-[N-(2-dimethylaminoethyl) carboxamido]-2[1H]-pyridone

N-(3-dimethylaminopropyl)-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy) phenylsulfonamide

N1-[3-(dimethylamino)propyl]-3-[3-chloro-5-(trifluoromethyl)-2-pyridyl] propanamide

3-(N-(2-dimethylaminoethyl)carboxamido]-1-(4-trifluoromethylbenzyl))-2 [1H]-pyridone

1-ethyl-3-(3-dimethylaminopropyl)urea

1-(3-(dimethylamino)-propyl)-3-phenylurea

N1-[2-(2,4-dichlorophenoxy)phenyl]-N2-[3-(dimethylamino)propyl] ethanediamide

N4-[3-(dimethylamino)propyl]-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide

N-[[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]carbonyl]-N'-[3-(dimethylamino)propyl]urea

N-(4-chlorophenyl)-N'-[3-dimethylaminopropyl]urea

N-(3,5-Dichloro-phenyl)-3-(3-dimethylamino-propylamino)-propionamide

[3-(2-Ethyl-6-methyl-pyridin-3-yloxy)-propyl]-dimethyl-amine

8-(3-Dimethylamino-propoxy)-1,3,7-trimethyl-3,7-dihydro-purine-2,6-dione

2-(3-Dimethylamino-propylamino)-isophthalonitrile

Dimethylamino-(3-methyl-benzo[b]thiophen-2-yl)-propan-1-one (HCl)

N-Benzo[1,3]dioxol-5-ylmethyl-N,N-dimethyl-propane-1,3-diamine

N,N-Dimethyl-N-(5-nitro-quinolin-8-yl)-propane-1,3-diamine

1-(4-Chloro-phenyl)-3-(3-dimethylamino-propyl)-urea

2-Amino-N-(3-dimethylamino-propyl)-benzamide

3-Phenyl-acrylic acid 3-dimethylamino-propyl ester

3,5-Dinitro-benzoic acid 2-dimethylamino-ethyl ester

[4-(4-Bromo-phenyl)-3-(3-dimethylamino-propyl)-3H-thiazol-2-ylidene]-phenyl-amine

3-Methyl-benzofuran-2-carboxylic acid dimethylamino-dimethyl-propyl ester

N'-(2-Chloro-4-nitro-phenyl)-N,N-dimethyl-propane-1,3-diamine

[3-(3-Dimethylamino-propyl)-5-(4-nitro-phenyl)-3H-thiazol-2-ylidene]-phenyl-amine

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-dimethyl-amine

2,3-Dimethyl-1H-indole-5-carboxylic acid 2-dimethylamino-ethyl ester

N'-(3,4-Dinitro-5-pyridin-2-yl-thiophen-2-yl)-N,N-dimethyl-propane-1,3-diamine

Cyclooctyl-dithiocarbamic acid 2-dimethylamino-ethyl ester (HCl)

N-(2,6-Difluoro-phenyl)-C-dimethylamino-acetamide

2-Acetylamino-3-(4-chloro-phenyl)-N-(3-dimethylamino-propyl)-acrylamide
N-[2-[5-(4-Bromo-phenyl)-furan-2-yl]-1-(3-dimethylamino-propyl carbamoyl)-vinyl]-4-methyl-benzamide
2,6-Bis-(3-dimethylamino-propylamino)-3-nitro-benzonitrile
N-[2-(2,4-Dichloro-phenoxy)-phenyl]-N'-(3-dimethylamino-propyl)-oxalamide
3,5-Dichloro-N-(3-dimethylamino-propyl)-2,6-dimethoxy-benzamide
2-Dimethylaminomethyl-3,4-dihydro-2H-naphthalen-1-one (HCl)
2-({1-[N-(3-Dimethylamino-propyl)-3-trifluoromethyl-phenyl]-methanimidoyl}-amino)-6-fluoro-benzoic acid
2,4-Dichloro-N-(3-dimethylamino-propyl)-N'-hydroxy-benzamidine
3-(3-Methyl-ureido)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide
5-Bromo-N-(3-dimethylamino-propyl)-2-hydroxy-benzamide
N-(2,4-Dichloro-phenyl)-6-(2-dimethylamino-ethylsulfanyl)-4-trifluoromethyl-nicotinamide
1-(2,6-Dichloro-benzyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide
3-Amino-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

12. Use according to any one of the preceding claims, wherein the medicament is for use as a vasodilator or to inhibit platelet aggregation.

13. Use according to claim 12, wherein the medicament is for use in the treatment or prevention of a peripheral vascular disease, glaucoma, age-related macular degeneration, preeclampsia, Raynaud's Syndrome, stroke or erectile dysfunction.

14. A method of treating a patient in need of an activator of soluble guanylate cyclase, which method comprises administering to said patient an effective amount of a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

15. A compound of the formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body by therapy.

16. A compound of the formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, excluding the following compounds:
2-Benzylsulfanyl-N-(3-dimethylamino-propyl)-benzamide
N-(3-Dimethylamino-propyl)-3-phenoxy-benzamide
1-(4-chlorobenzyl)-3-(2-N,N-dimethylethylamido)-6-pyridone
1-(2,6-dichlorobenzyl)-3-(3-N,N-dimethylpropylamido)-6-pyridone
1-(3-trifluoromethylbenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone
1-(2,6-dichlorobenzyl)-3-(2-N,N-dimethylethylamido)-2-pyridone
1-(3,4-dichlorobenzyl)-3-(N-[2,N,N-dimethylaminoethylamido])-2-pyridone
1-(2,6-dichlorobenzyl)-3-(N-[2-N,N-dimethylaminoethylamido])-6-pyridone
5-chloro-1-(3,4-dichlorobenzyl)-3-(2-N,N-dimethylaminoethylamido)-6-pyridone
5-chloro-3-(2-N,N-dimethylaminoethylamido)-1-(3-trifluoromethylbenzyl)-6-pyridone
5-chloro-1-(3,4-dichlorobenzyl)-3-N-(2-[N',N'-dimethylaminoethylamido])-2-pyridone
5-chloro-1-(4-chlorobenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl)amido-2-pyridone
5-chloro-1-(3-trifluoromethylbenzyl)-3-N-(2-(N',N'-dimethylamino)ethyl) amido-2-pyridone

1-benzyl-5-chloro-3-N-(2-[N',N'-dimethylamino]ethyl)carboxamido-6-pyridone

5-chloro-1-(4-chlorobenzyl)-3-N-(2-[N',N'-dimethylamino]ethyl) carboxamido-6-pyridone

4-(2,4-dichlorobenzoyl)pyrrole-2-N-dimethylaminopropylcarboxamide

4-[(N-[3-(N',N'-dimethylaminopropyl)]carboxamido]-2-phenylthiazole

4-(N-(3-N',N'-dimethylaminopropyl)carboxamido)-2-(4-pyridinyl)thiazole

2-[4-(N-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl-4-(3-trifluoromethylphenyl]thiazole

4-(4-chlorophenyl)-2-(4-[3-N',N'-dimethylaminopropyl]carboxamido)phenyl) thiazole

1-(3,5-bis(trofluoromethyl)benzyl)-3-[N-(2-dimethylaminoethyl) carboxamido]-2[1H]-pyridone

N-(3-dimethylaminopropyl)-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy) phenylsulfonamide

N1-[3-(dimethylamino)propyl]-3-[3-chloro-5-(trifluoromethyl)-2-pyridyl] propanamide

3-(N-(2-dimethylaminoethyl)carboxamido]-1-(4-trifluoromethylbenzyl))-2 [1H]-pyridone

1-ethyl-3-(3-dimethylaminopropyl)urea

1-(3-(dimethylamino)-propyl)-3-phenylurea

N1-[2-(2,4-dichlorophenoxy)phenyl]-N2-[3-(dimethylamino)propyl] ethanediamide

N4-[3-(dimethylamino)propyl]-3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamide

N-[[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]carbonyl]-N'-[3-(dimethylamino)propyl]urea

N-(4-chlorophenyl)-N'-[3-dimethylaminopropyl]urea

N-(3,5-Dichloro-phenyl)-3-(3-dimethylamino-propylamino)-propionamide

[3-(2-Ethyl-6-methyl-pyridin-3-yloxy)-propyl]-dimethyl-amine

8-(3-Dimethylamino-propoxy)-1,3,7-trimethyl-3,7-dihydro-purine-2,6-dione

2-(3-Dimethylamino-propylamino)-isophthalonitrile

Dimethylamino-(3-methyl-benzo[b]thiophen-2-yl)-propan-1-one (HCl)

N-Benzo[1,3]dioxol-5-ylmethyl-N,N-dimethyl-propane-1,3-diamine

N,N-Dimethyl-N-(5-nitro-quinolin-8-yl)-propane-1,3-diamine

1-(4-Chloro-phenyl)-3-(3-dimethylamino-propyl)-urea

2-Amino-N-(3-dimethylamino-propyl)-benzamide

3-Phenyl-acrylic acid 3-dimethylamino-propyl ester

3,5-Dinitro-benzoic acid 2-dimethylamino-ethyl ester

[4-(4-Bromo-phenyl)-3-(3-dimethylamino-propyl)-3H-thiazol-2-ylidene]-phenyl-amine

3-Methyl-benzofuran-2-carboxylic acid dimethylamino-dimethyl-propyl ester

N'-(2-Chloro-4-nitro-phenyl)-N,N-dimethyl-propane-1,3-diamine

[3-(3-Dimethylamino-propyl)-5-(4-nitro-phenyl)-3H-thiazol-2-ylidene]-phenyl-amine

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-dimethyl-amine

2,3-Dimethyl-1H-indole-5-carboxylic acid 2-dimethylamino-ethyl ester

N'-(3,4-Dinitro-5-pyridin-2-yl-thiophen-2-yl)-N,N-dimethyl-propane-1,3-diamine

Cyclooctyl-dithiocarbamic acid 2-dimethylamino-ethyl ester (HCl)

N-(2,6-Difluoro-phenyl)-C-dimethylamino-acetamide

2-Acetylamino-3-(4-chloro-phenyl)-N-(3-dimethylamino-propyl)-acrylamide

N-[2-[5-(4-Bromo-phenyl)-furan-2-yl]-1-(3-dimethylamino-propylcarbamoyl)-vinyl]-4-methyl-benzamide

2,6-Bis-(3-dimethylamino-propylamino)-3-nitro-benzonitrile

N-[2-(2,4-Dichloro-phenoxy)-phenyl]-N'-(3-dimethylamino-propyl)-oxalamide

3,5-Dichloro-N-(3-dimethylamino-propyl)-2,6-dimethoxy-benzamide

2-Dimethylaminomethyl-3,4-dihydro-2H-naphthalen-1-one (HCl)

2-({1-[N-(3-Dimethylamino-propyl)-3-trifluoromethyl-phenyl]-methanimidoyl}-amino)-6-fluoro-benzoic acid

2,4-Dichloro-N-(3-dimethylamino-propyl)-N'-hydroxy-benzamidine

3-(3-Methyl-ureido)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

5-Bromo-N-(3-dimethylamino-propyl)-2-hydroxy-benzamide

N-(2,4-Dichloro-phenyl)-6-(2-dimethylamino-ethylsulfanyl)-4-trifluoromethyl-nicotinamide

1-(2,6-Dichloro-benzyl)-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid (2-dimethylamino-ethyl)-amide

3-Amino-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid (3-dimethylamino-propyl)-amide

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 00/04249

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/84 C07C235/50 C07C235/60 C07D213/82 C07C233/78
C07C235/82 C07D307/68 C07C275/36 C07C275/38 C07C275/24
A61K31/165 A61K31/455 A61K31/34 A61K31/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 56 388 A (HOECHST MARION ROUSSEL DE GMBH) 24 June 1999 (1999-06-24) page 1; line 44 - line 48; claims 1,5-7; examples 11,18,27,40,63 ---	1-3,5,7, 8,12-16
X	FR 2 670 780 A (SYNTHELABO) 26 June 1992 (1992-06-26) see compounds in the table and the corresponding intermediates according to formula II in annex 1	15,16
A	see page 12, lines 1-30 --- -/--	12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2001	30. 01. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seufert, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CATANESE B ET AL: "EFFECTS OF BENZYDAMINE AND OTHER NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON PLATELET AGGREGATION INDUCED BY: ARACHIDONIC ACID, ADP AND COLLAGEN" BOLLETTINO CHIMICO FARMACEUTICO,IT,SOCIETA EDITORIALE FARMACEUTICA, MILANO, vol. 125, no. 7, 1986, pages 228-233, XP000879042 ISSN: 0006-6648 page 228, right-hand column, line 9 - line 14	15,16
A		12
X	US 2 777 853 A (N. STEIGER, N. J. NUTLEY) 15 January 1957 (1957-01-15) column 2, line 33 - line 41; claim 1; examples	15,16
X	DE 19 26 754 A (LABORATOIRES JAQUES LOGEAIS) 16 July 1970 (1970-07-16) claims 1,19,20; examples	15,16
X	DE 11 56 080 B (LÄÄKETEHDAS ORION OY) examples	15,16
X	US 3 170 955 A (R. K. RICHARDS ET AL.) 23 February 1965 (1965-02-23) column 1, line 24 - line 28; examples	15,16
X	HITOSHI UNO ET AL.: "Studies on 3-Substituted 1,2-Benzisoxazole Derivatives 6. Synthesis of 3-(sulfamoylmethyl)-1,2-benzisoxazole Derivatives and Their Anticonvulsant Activities" J. MED. CHEM., vol. 22, no. 2, 1979, pages 180-3, XP000973082 see table I, compound n	15,16
X	DATABASE BEILSTEIN 'Online! Beilsteininformationssysteme; XP002156963 see abstract and substance 2128951 & J. MED. CHEM., vol. 24, no. 7, 1981, pages 798-06,	15,16
X	DE 10 20 636 B (J. R. GEIGY A.-G.) examples	16
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 28 47 792 A (LEO PHARM PROD LTD) 10 May 1979 (1979-05-10) see table page 23, example 5	16
X	US 2 553 093 A (R. M. JACOB ET AL.) 15 May 1951 (1951-05-15) see column 4, lines 36-37, 70-71, column 5, lines 8-9, 28-29 and examples XVIII and XIX , intermediates corresponding to the intermediate described in column 5, line 28-29, column 6, lines 47-48	16
X	US 2 628 224 A (TH. LE SUEUR CAIRNS, J. C. SAUER) 10 February 1953 (1953-02-10) see colum 5, table left side	16
X	DATABASE BEILSTEIN 'Online! Beilsteininformationssysteme; XP002156964 see substance BRN 1735535 & J. AM. CHEM. SOC., vol. 77, 1955, page 4599	16
X	DATABASE BEILSTEIN 'Online! Beilsteininformationssysteme; XP002156965 see substance BRN 1698161 & J. AM. CHEM. SOC. , vol. 74, 1952, page 1313	16
X	DATABASE BEILSTEIN 'Online! Beilsteininformationssysteme; XP002156966 see substance BRN 165200 & C.R. HEBD. SEANCES ACAD. SCI., vol. 244, 1957, page 1791, 1792	16
X	DATABASE BEILSTEIN 'Online! Beilsteininformationssysteme; XP002156967 see substance BRN 3286902 & J. CHEM. AM. SOC., vol. 78, 1956, page 6123, 6125	16
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN 'Online! Beilsteininformationssysteme; XP002156969 see substance BRN 216878 & J. AM. CHEM. SOC., vol. 66, 1944, page 540 ---	16
A	EP 0 908 456 A (HOECHST MARION ROUSSEL DE GMBH) 14 April 1999 (1999-04-14) page 2, line 44 - line 21; claims 1,10,11 ---	1-14
A	US 5 478 956 A (OTTOW ECKHARDT ET AL) 26 December 1995 (1995-12-26) column 3, line 21 -column 4, line 42; claims 1,8 ---	1-14
P,X	WO 00 27394 A (GLEN ROBERT ;MADGE DAVID (GB); SELWOOD DAVID (GB); UNIV LONDON (GB) 18 May 2000 (2000-05-18) the whole document ---	1-16
P,X	DE 198 36 697 A (HOECHST MARION ROUSSEL DE GMBH) 17 February 2000 (2000-02-17) page 7, line 52 - line 65; claims 1,9-12; example 105 -----	1-3,7,8, 12-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/04249

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search for claims 15 and 16 revealed a very large number of documents relevant to the issue of novelty (a random selection has been cited in the search report). So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.
Furthermore, the present claims 1-14 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
As a consequence of the aformentioned objections, the search has been concentrated on those parts of the claims which appear to be supported and disclosed, namely those parts relating to compounds of the following general formula -C(=O)N-CH2-CH2-CH2-NR1R2 wherein R1/R2 are at least CH2 or form a ring together form a carbocyclic ring.
Despite the limitation too many documents were retrieved which are relevant to the issue of novelty of claim 15 and 16. Therefore, neither the search nor the search report may be considered complete for those claims. The documents cited for claims 15 and 16 are merely a random selection of the relevant documents.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 00/04249

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]al Application No
PCT/GB 00/04249

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